2017-2038

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

(Serial No. 12/726,158)

IN RE MANUEL MARQUEZ
AND SAMANTHA MARQUEZ,
Appellants.

Appeal from the United States Patent and Trademark Office,
Patent Trial and Appeal Board

CORRECTED APPEAL BRIEF OF APPELLANTS MANUEL MARQUEZ AND SAMANTHA MARQUEZ

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CERTIFICATE OF INTEREST

Counsel for Appellants certifies the following:

1. The full name of every party or amicus represented by me is:

Manuel Marquez and Samantha Marquez

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Manuel Marquez and Samantha Marquez

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Not Applicable

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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Date: September 27, 2017

/s/ Matthew J. Dowd
Signature of counsel

Matthew J. Dowd
Printed name of counsel

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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule. 47.5, there are no related appeals, and counsel is unaware of any court cases that may be affected by this appeal. Two related patent applications (Ser. Nos. 15/606,042 and 15/606,027) are currently pending at the U.S. Patent and Trademark Office.

STATEMENT OF JURISDICTION

This is an appeal from a final decision of the Patent Trial and Appeal Board. The Board's decision was dated March 15, 2017. Appx0001. A notice of appeal was timely filed on May 11, 2017. Appx0051. This Court has jurisdiction under 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. § 141.

STATEMENT OF THE ISSUES

1) Whether the Patent Trial and Appeal Board ("the Board") reasonably construed the claim terms "artificial gland," "assembled in three dimensions in a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer," and "bio-reactor."

2) Whether the Board correctly held that claims 1–4, 7, and 35 are not directed to patent-eligible subject matter under 35 U.S.C. § 101.

3) Whether the Board correctly found that claims 1, 2, 4, 7, and 35 are anticipated under 35 U.S.C. § 102.

4) Whether the Board correctly held that claims 1, 2, 4, 7, and 35 are obvious under 35 U.S.C. § 103.

5) Whether the Board correctly found that the application failed to set forth a specific and substantial utility and whether the Board correctly held that claims 1–5, 7, 8, 13, and 31–36 are not enabled under 35 U.S.C. § 112.

6) Whether the Board correctly found that claims 1–5, 7, 8, and 13 are not patentable for failure to comply with the written description requirement under 35 U.S.C. § 112 based on the claim construction of the terms "comprising," "independent unit," and "isolated product."

STATEMENT OF THE CASE AND FACTUAL BACKGROUND

I. Procedural Background

This appeal is from the Board's March 15, 2017 decision, which affirmed-in-part and reversed-in-part the examiner's rejections and ruled that all pending claims were not patentable. A brief procedural summary of the prosecution history is provided.

The nonprovisional patent application was filed on March 17, 2010, and claims priority to two provisional applications filed in March and April 2009. Appx0080. The first substantive office action on the merits was issued on June 29, 2012, rejecting certain then-pending claims as anticipated and/or non-enabled. Appx1000–1006. On December 26, 2012, the applicants (collectively "Marquez") filed a response, along with an affidavit under Rule 1.132, and amended certain claims. Appx0980–0999; Appx0672–0678. The examiner then issued a final office action dated May 16, 2012, maintaining the same rejections. Appx0972–0979.

Marquez then filed a notice of appeal to the Board and included a detailed attachment to the pre-appeal brief request for review. Appx0964–0970. In response, the PTO withdrew the rejections and reopened prosecution. Appx0962–0963. This was followed by an office action, dated June 3, 2014, rejecting the claims under § 101, § 102(b), § 103(a), § 112 (enablement), and § 112 (indefiniteness). Appx0945–0961. On July 14, 2014, Marquez replied with a detailed response and an amendment of certain claims. Appx0909–0944. On December 3, 2014, the examiner issued a final office action, rejecting the claims under § 101,

§ 102(b), § 103(a), and § 112 (enablement and written description). Appx0876–0908.

Marquez then filed a second notice of appeal to the Board, Appx0874, which led to briefing before the Board, Appx0688–0873, and then the Board's final decision, Appx0001–0050.

II. Factual Background

A. The Claimed Invention is Directed to Novel, Artificial Gland-Like Constructs Called Celloidosomes®

The claimed invention is directed to an artificial cell-based construct inspired by the structure and function of a biological gland. Appx0084–0086. The "artificial gland" construct is analogous to "a 'living capsule' with a biomembrane (tissue) shell and a unique core that acts as container or reservoir." Appx0082. It is created by a synthetic process that that assembles individual cells int a unique membrane-based structure having a "bio-reactor" reservoir. Appx0082. The artificial cell-based constructs are called Celloidosomes®.

Claim 1 reads as follows:

> 1. An artificial gland comprising an independent unit for promoting biological activity, the independent unit consisting of an isolated product, the artificial gland further comprising:
>
> cells assembled in three dimensions in a component selected from the group consisting of a flow chamber, a microfluidic

device, and an ink jet printer, the cells organized to form a membrane, the membrane configured to define an enclosed volume; and,

a reservoir within the enclosed volume, the reservoir comprising a bio-reactor containing a product of activity of the cells.

Appx0003; Appx0057.

As another exemplar, claim 35 reads as follows:

35. An artificial gland that is an independent micro-scale unit for promoting biological activity, the artificial gland comprising:

cells assembled in three dimensions and organized to form a membrane, the membrane defining an enclosed micro-scale volume; and

a reservoir within the enclosed micro-scale volume, the reservoir comprising volvox algae.

Appx0078.

Certain claims cover Celloidosomes® that are constructed from cellular components, such as proteins, instead of whole cells. Appx0077–0078. For example, claim 33 reads:

An artificial gland of micro-scale for promoting biological activity, the artificial gland comprising:

components of a cell assembled in three dimensions and organized to form a membrane, the membrane defining an enclosed micro-scale volume; and,

a reservoir within the enclosed micro-scale volume, the reservoir comprising a bio-reactor containing a product of

activity of the components of a cell, wherein the reservoir comprises a substance selected from the group consisting of a gas, a liquid, and a gel.

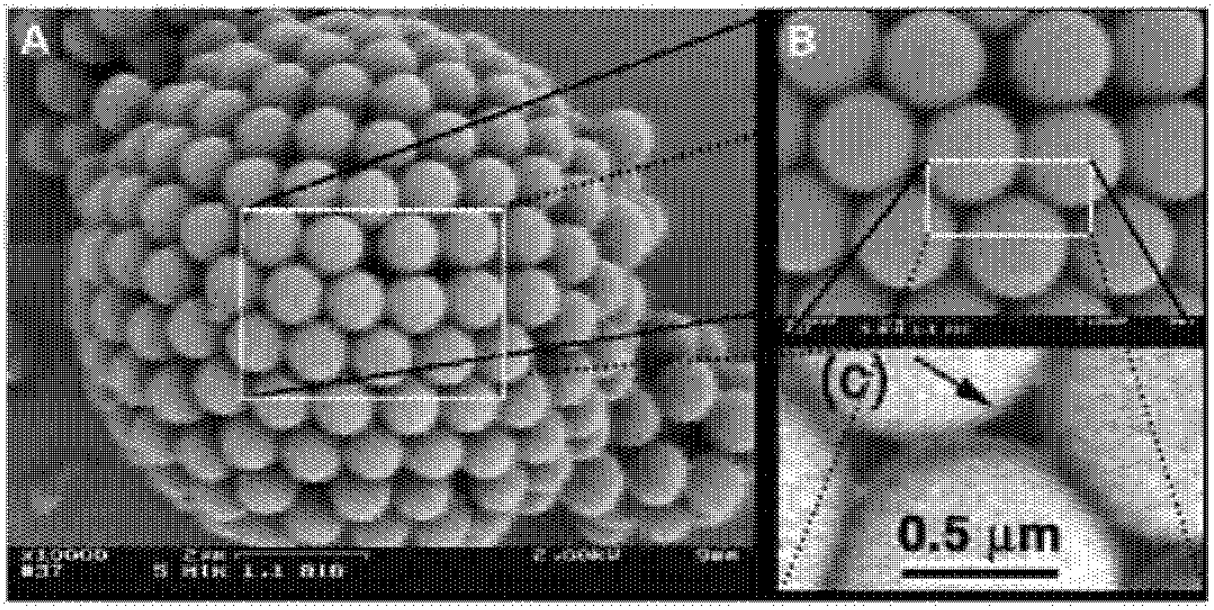
Appx0077. Other pending claims, Appx0057–0079, are presented below in context with the relevant rejections.

B. Samantha Marquez and Her Co-Inventors Created Celloidosomes® as an Improvement over the Prior Art Colloidosomes

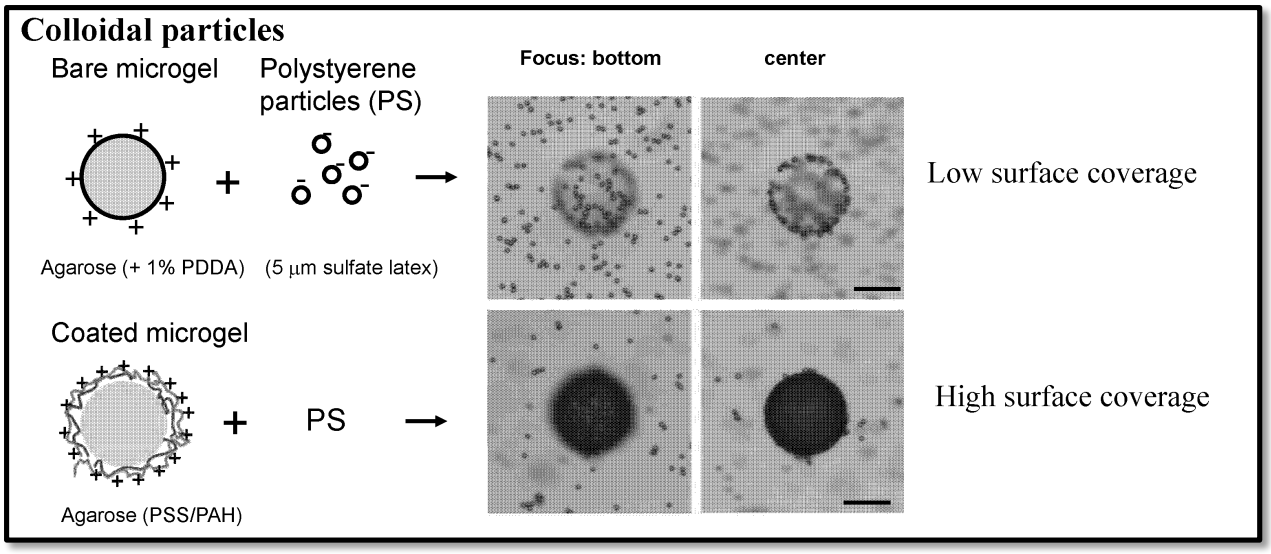
Before the invention, there were no synthetically assembled constructs of living cells that could be used as potential drug carriers, biological microreactors, or templates for tissue engineering. *See* Appx0080–0084. The absence of assembled biological constructs made of living cells was a noted problem in the field of synthetic biology. One prior art report observed that "the precise and controllable fabrication of biomaterials from live cells still remains one of the most promising, yet largely unrealized, applications of colloidal assembly." Appx0307.

There were, however, synthetic microcapsules made from various chemical subunits. Appx0267. These synthetic microcapsules were referred to as "colloidosomes." Appx0212; Appx0201; Appx0268. Colloidosomes are similar to emulsions, *see* Appx0508, and were sometimes called "armored bubbles," Appx0202.

Colloidosomes are generally synthetic constructs made from colloidal subparticles comprising specific chemicals. Appx0212; Appx0359. The colloidal subparticles can be a variety of chemicals. Appx0201; Appx0202; Appx0212; Appx0215; Appx0307; Appx0508. Magnified many times, a colloidosome may resemble a ball made up of smaller balls, as shown in the following micrograph of a colloidosome assembled from 900 nm diameter polystyrene spheres:



Appx0212; Appx0316. Another schematic in the record depicts the electrostatic interactions used to construct colloidosomes:



Appx0216.

Colloidosomes and related emulsion-based systems have numerous real-world uses, including for the "preparation of microcapsules with controlled permeability for the programmed release of encapsulated drugs and the targeted delivery of pharmaceuticals." Appx0267 (footnotes omitted); *see also* Appx0225; Appx0503–0512. Even so, chemical-based colloidosomes had inherent limitations, and there was a need for cell-based alternatives to colloidosomes. Appx0081–0082.

As the improvement, Samantha Marquez and her co-inventors designed and created cell-based, assembled constructs they called "artificial glands," also known as Celloidosomes®.[1] Appx0199–0223;

[1] *See* Appx0359 (identifying U.S. trademark Registration Nos. 3,738,109 and 3,828,107). During the pendency of the present matter, the

Appx0302–0305; Appx0359–0369; Appx0742. Celloidosomes® are similar in structure to chemical-based colloidosomes, except that, instead of chemical colloidal units, individual living cells (or cellular components) are physically assembled into the structure of the Celloidosomes®. Appx0199–223; Appx0302–0305; Appx0359–0369.

The assembly of Celloidosomes® uses a process that starts with individual, isolated cells. Appx0360–0367. The cells, such as yeast or red blood cells, are first assembled into membranes. Appx0089; Appx0302–0305. The membranes are then physically manipulated to form the final Celloidosomes®. Appx0089. Celloidosomes® may also be constructed from cellular components. Appx0095. Celloidosomes® are, in a way, "living capsules"—an artificially-assembled membrane of functional cells configured in a unique microshape and having an interior bioreactor. Appx0090.

The interior volume creates a "micro-container", or a "bioreactor," which is "a manufactured or engineered device or system that supports a biologically active environment." Appx0090; Appx0924; Appx0202;

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registration of the mark lapsed and is now subject to a new pending trademark application (Ser. No. 87368768).

Appx0432–0434. The interior volume can be a gas, liquid, gel, or some combination. Appx0090. In certain instances, the interior volume can contain other intact cells. *Id.* The bioreactor also contains "a product of activity of the cells" of the artificial gland. *Id.*

C. The Inventors Have Presented Their Research Nationally and Internationally and Published It in Peer-Reviewed Research Journals

The inventors presented and published their Celloidosomes® research at national and international meetings and in peer-reviewed journals. *See* Appx0199–223; Appx0302–0305; Appx0359–0369. Their most recent publication, in 2013, summarized their work involving "a glass-based microfluidic route for the generation of a particular class of celloidosomes consisting of an assembly of yeast cells at the outskirts of liquid drops inside an also liquid continuous phase." Appx0302. Another of their research articles explored a subset of Celloidosomes® called "yeastosomes" that were "based on self-assembly of yeast cells onto liquid-solid or liquid-gas interfaces." Appx0201; *see also* Appx0211; Appx0217; Appx0221.

The primary inventor, Samantha Marquez, has received wide-spread recognition for the Celloidosomes® invention. Samantha was

profiled in several reports, including an NBCLatino report and a special report by CNN's Dr. Sanjay Gupta. Appx0742.[2] In her CNN interview, Samantha explained the motivation for creating Celloidosomes® and some of the likely uses for the artificial cellular constructs. *Id.*

Other researchers have subsequently performed independent research on Celloidosomes®. Appx0267–0277. One United Kingdom group reported that Celloidosomes® "may find applications as drug carriers, biological microreactors, and templates for tissue engineering." Appx0268. Their report also taught that Celloidosomes® "may be used as a simple model of colonial microorganisms and serve as a starting point for development of artificial symbiotic multicellular organisms." *Id.*[3]

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[2] The record cites http://nbclatino.com/2013/10/08/innovators-samantha-marquez/ and http://edition.cnn.com/videos/international/2014/07/17/spc-vital-signs-medical-discoveries-b.cnn. The CNN profile details the genesis and development of the Celloidosomes® artificial gland.

[3] The UK researchers acknowledged Marquez's earlier work in a footnote: "While this paper was under review we became aware that the company YNANO LLC, Midlothian, VA, USA has registered as trademarks Celloidosome® and Cellosome®." Appx0277, n.25. The present patent application was originally assigned to YNANO. *See* Appx1035.

D. The Inventors Filed Patent Applications to Protect Their Novel Cell-Based Constructs

Having constructed their novel, artificially-assembled Celloidosomes®, Samantha Marquez and her co-inventors filed for patent protection. Appx0080–0173. Marquez filed two U.S. provisional applications in 2009 and then a U.S. non-provisional application on 2010. Appx0080–0173; Appx1035–1035.

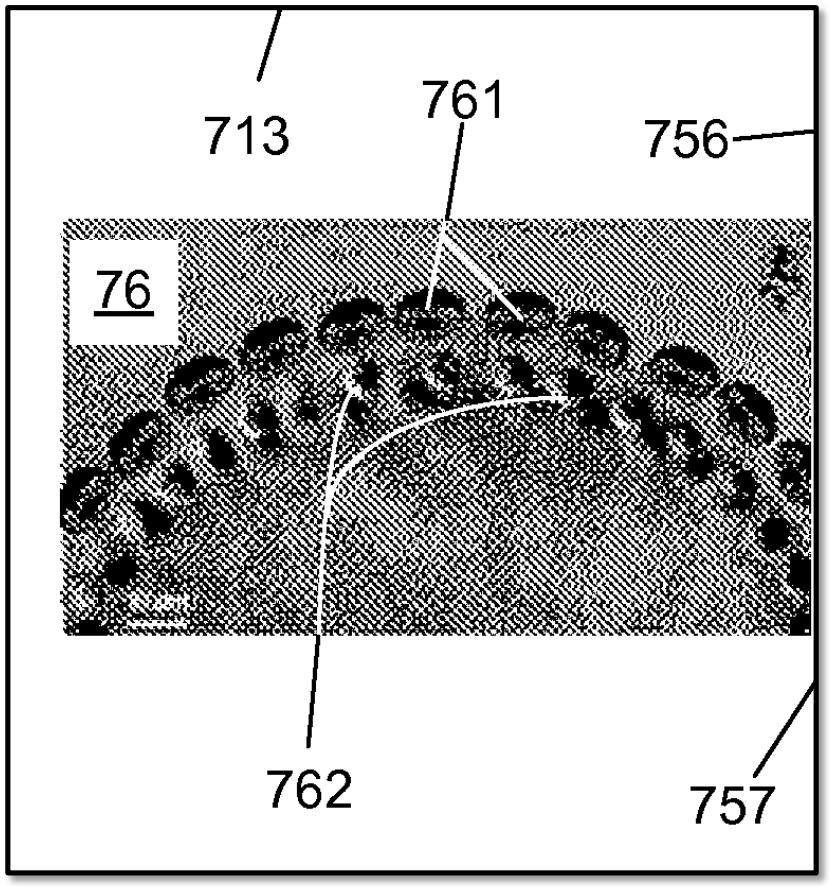
Marquez's application explained that "[t]he current state-of-the-art does not allow for control over the proper arrangement of multiple types of cellular and subcellular units in three dimensions." Appx0084. The application also taught that the invention "can be used [to] accomplish precise control of the spatial arrangement of cells as well as segregation and assembly of different types of cells." Appx0085. The application thus provided "an artificial means to arrange cells, biological units and subcellular structures similarly to natural multicellular organism development, while adding capability to control spatial location and confinement through the use of external fields, microfluidic channels, and solvent-phase partitioning." Appx0085.

As the application explains, "[t]he self-assembly of cells at the liquid/liquid interface is driven by the minimization of the interfacial

energy and is enhanced by electrostatic interaction." Appx0110. This interaction differs from what occurs in naturally-grown cellular structures, which require complex extracellular matrices. *See* Appx0011; Appx0119; Appx0256. For instance, "[c]ells grown in tissue culture flasks interact with the protein molecules adsorbed to the rigid flask surface." Appx0187. In other instances, "many microbes in their natural habitats are found in biofilm ecosystems" and "[c]ells in these biofilms are embedded within a matrix of extracellular polymeric material." Appx0256; *see also* Appx0187 (describing the extracellular matrix for endothelial cells).

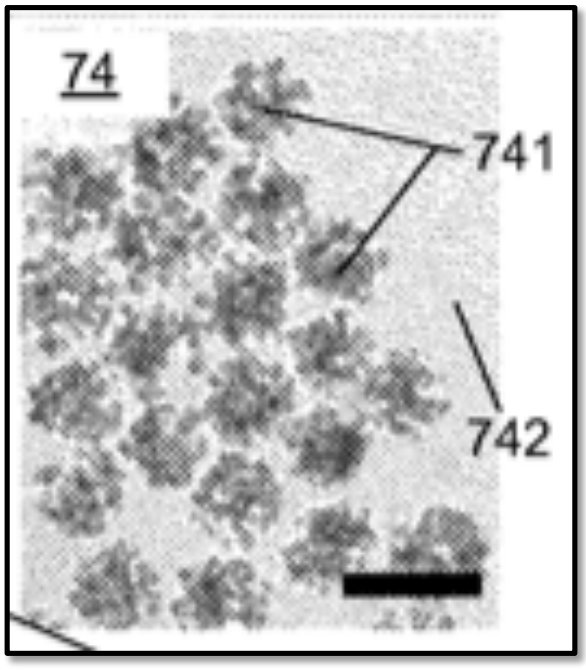
Marquez's application described numerous embodiments of Celloidosomes®. Appx088–0146; Appx0162–0173. The application also contained micrographic images of Celloidosomes® that were prepared using the techniques disclosed in the application. Appx0168. Some examples were prophetic; others were reduced to practice. Appx0168. The application also offered various methods of making different types of the artificial constructs, including using electrostatic interactions, electrocoalescene, polymer monolayer methods, combining droplets in microchannels, and a double emulsion methods. Appx0098–0127.

One Celloidosomes® construct used red blood cells to create an artificial gland surrounding a volvox algae colony. Appx0120. In the following image, the red blood cells (761) are arranged in an ordered fashion around the volvox algae colony (762).



Appx0168; Appx0120.

Another embodiment created an artificial gland using a droplet, electrocoalescence, and controlled gelation method, as shown in the following image.



Appx0097; Appx0099–0100; Appx0168.

After the examiner issued a restriction requirement in Marquez's application, Appx1013–1023, Marquez elected to proceed with the examination of the subset of claims at issue in this appeal, Appx1007–1012.

E. The PTO and the Board Rejected the Claims Based on Numerous Grounds, Some of Which Are Internally Inconsistent

Throughout the prosecution, the PTO viewed the claimed artificial constructs as not patentable in view of naturally occurring cells and organisms or in view of cell structures that were cultured in a growth medium from an individual cell. *See, e.g.*, Appx0789.

1. The first office action rejected the claims under § 102 and § 112 (enablement)

After Marquez elected to proceed with select claims, the examiner rejected all of the then-pending claims as anticipated under § 102 and not enabled under § 112. Appx1001–1006. For the anticipation rejection, the examiner pointed to a human blastocyst, *i.e.*, a fertilized egg developing into a human embryo. Appx1004; Appx0471–0480.

For the enablement rejection, the examiner asserted that "[t]he claims are to 'an artificial gland,' but there is no evidence the cell[-]containing w/o/w or o/w/o emulsion behaves like a gland." Appx1004. Looking past the application's written description, the examiner targeted the term "gland," arguing that "[g]lands secrete molecules that have action elsewhere," but "[t]here is no evidence the emulsions claimed have the ability to secrete molecules into a system, such as a body, where the molecules affect biological functions at other system locations." Appx1004–1005.

The examiner also noted several structural differences between the claimed Celloidosomes® and naturally occurring glands. Appx1005.

> Further the claims require a membrane of living cells, but such a structure is not evident. To form membrane, the cells would need to be embedded into an extracellular matrix or

> some other membranous structure. Cells are only part of a biological membrane. Algal and bacterial cells, as examples, would not form a membranous structure as they do not secrete the proper proteins in which they could embed.

Appx1005.

In response, Marquez amended certain claims to clarify that "the bioreactor contain[s] a product of activity of the cells in the surrounding membrane." Appx0995. Marquez also distinguished the human blastocyst from the claimed invention and explained how the claims are enabled, for example, by reference to specific examples in the patent application. Appx0996–0999. Marquez explained, for example, that the examiner's "findings about the need for an 'extracellular matrix or some other membranous structure,' other than the gel, droplet or bubble specified in the claimed methods, are unsupported assertions that are contrary to the experimental results achieved by applicant." Appx0998.

Marquez supported the response with a Rule 1.132 declaration by Dr. Zhengdong Cheng. Appx0672–0687. Dr. Cheng is a Professor in the Artie McFerrin Department of Chemical Engineering at Texas A&M University. Appx0672. He earned a Ph.D. in physics from Princeton University, as well as master's and undergraduate physics degrees in his native China. Appx0676. His experience includes postdoctoral positions

at Harvard University and ExxonMobil Research & Engineering. Appx0676. At the time, Dr. Cheng had 67 publications in refereed proceedings, four books, three book chapters, two invited review articles, and three U.S. patents. Appx0679.

Dr. Cheng stated that he had been retained without compensation and had read the patent application and the office action. Appx0673. He opined on the claimed invention and the cited art:

> The examples cited by examiner involving "[a]lgal and bacterial cells" is not correct in that they have been experimentally produced by my research group as well as other research group in the US, Japan and Europe. We have experimental evidence that Fungi, Algae, Bacteria and also a diverse group of mammalian Cells (NIH-3T3, Cortical Cells, HEP-G2, etc.) can be 'self-assembled' in liquid-liquid interfaces from multiple emulsions. Also those cells can be self-assembled on gas-liquid interfaces of microbubbles, to form stable micro-core/shell tissues as described by Marquez, et al in their patent application.

Appx0673.

Dr. Cheng identified nine research publications and presentations that reported on the work being claimed in Marquez's application. Appx0674. Dr. Cheng added that "[s]imilar experimental evidence has been provided by: Prof. Alberto Fernandez-Nieves (Georgia Tech) Prof. David Weitz (Harvard), Tommy Angelini (U. of Florida)." Appx0674.

2. The second office action maintained the § 102 and § 112 rejections

In May 2013, the examiner issued a final office action. Appx0971–0979. The examiner maintained the previous rejections under § 102 and § 112. *Id.*

With the enablement rejection, the examiner again imposed a requirement that the claimed artificial gland must "behave[] like a gland." Appx0975. The examiner also argued that "there is no evidence that the artificial glands release any such substances in regulated or controlled manner," without identifying any such requirement in the claim. Appx0977.

The examiner dismissed Dr. Cheng's declaration, responding that the "[d]eclarant never states the artificial glands exhibit regulated or controlled release of any substance contained in the reservoir or core." Appx0978. The examiner was similarly unimpressed by Marquez's submitted references in support of enablement, stating that they "do not teach the regulated or controlled release of any substance from the reservoir or core." Appx0978. In sum, the examiner concluded that "[t]he products claimed therefore do not meet any criteria for being a 'gland.'" Appx0978.

In response, Marquez filed a notice of appeal to the Board, along with a five-page attachment identifying numerous errors with the examiner's findings and conclusions. Appx0964–0970.

3. The PTO withdrew the rejections and issued a third office action based on § 101, § 102, § 103, and § 112 (enablement and indefiniteness)

The PTO next withdrew the rejections and reopened prosecution. Appx0963. The examiner issued a non-final office action, rejecting all pending claims based on one or more of § 101, § 102, § 103, and § 112 enablement and indefiniteness. Appx0946–0961.[4]

Relevant here, the examiner now contended that "[t]he artificial gland fails to exhibit any differences from naturally occurring aggregates of cells." Appx0948. This new position contrasted with the examiner's earlier conclusion that, in nature, "a membrane of living cells" requires "an extracellular matrix or some other membranous structure," Appx1005, which is not present in Marquez's invention.

The examiner identified three references—Zetter, Debnath, and Kirk—as a basis for the examiner's belief that the claimed artificial

[4] The indefiniteness rejection was withdrawn and is not at issue on appeal.

glands "are found in nature." Appx0949. The claims, according to the examiner, covered naturally occurring biological structures, despite the claim's requirement that the claimed structure was "artificial" and "assembled" from individual cells. *See, e.g.*, Appx0057–0059.

Zetter discloses a 4-day mouse blastocyst, as depicted in the following drawing:

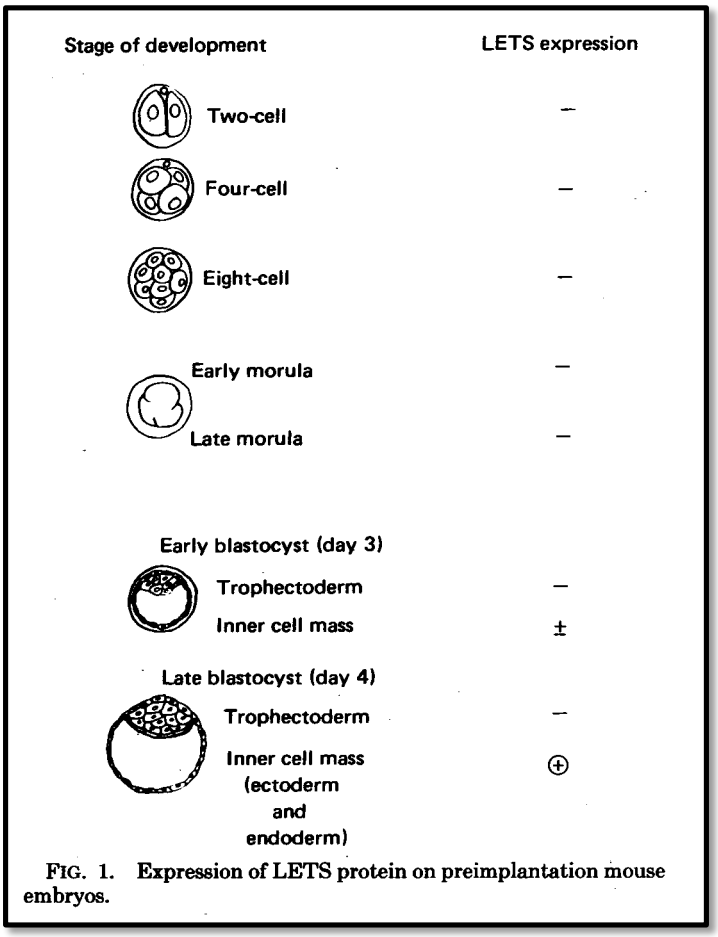
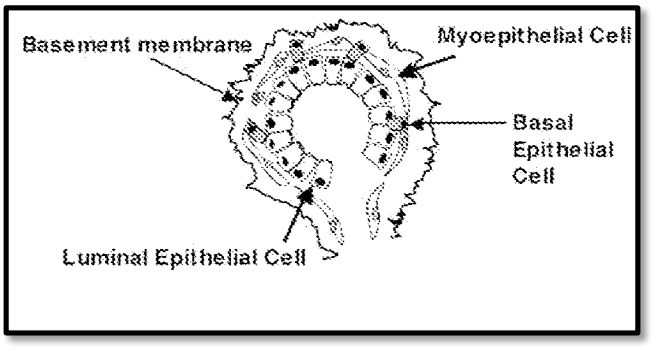


FIG. 1. Expression of LETS protein on preimplantation mouse embryos.

Id.; Appx0590–0594. Zetter reports on "[t]he expression of a high molecular weight cell surface glycoprotein (LETS, fibronectin) by

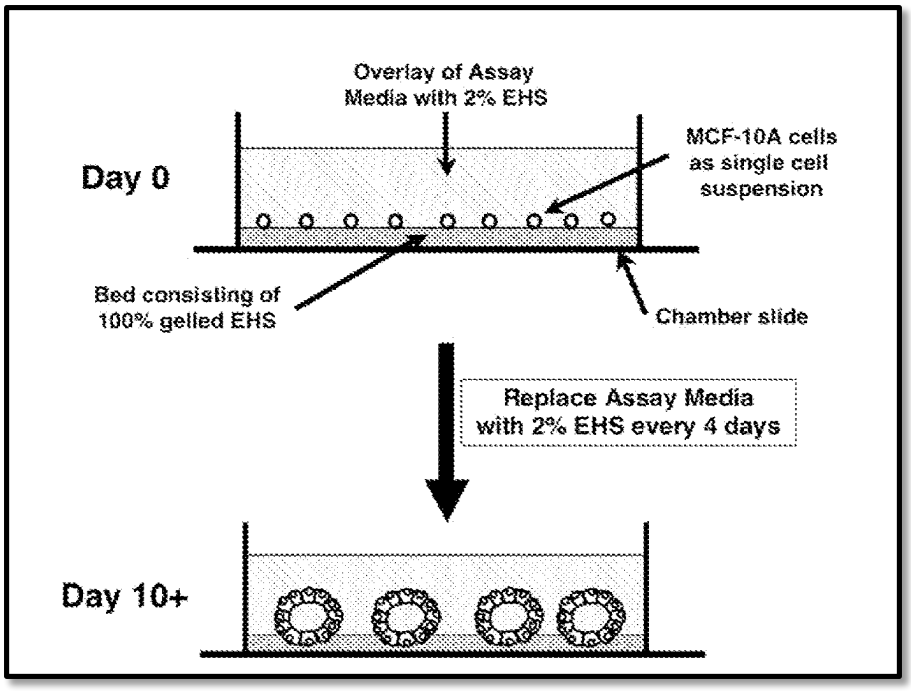
preimplantation mouse embryos" and notes that LETS protein "can have an important role in mediating cell-substratum adhesion" and "has been implicated as a mediator of certain types of cell-cell interactions." Appx0590.

Debnath discloses a schematic of a lobule of a human mammary gland.



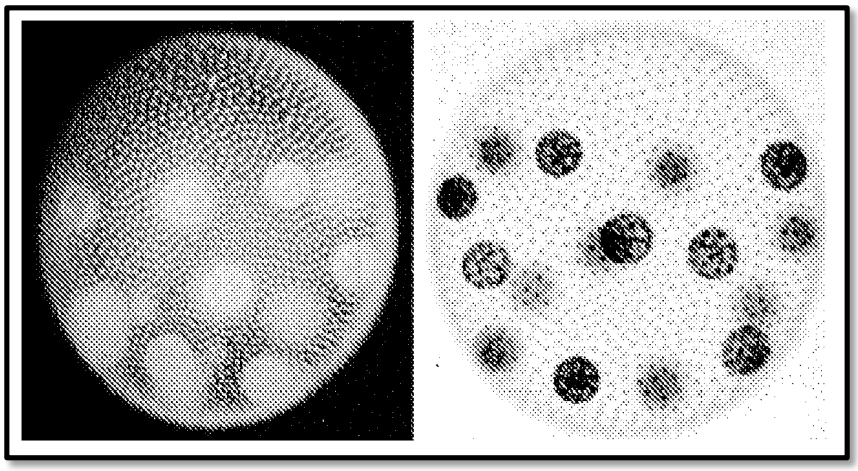
Appx0230. Debnath also reports on mammary acini cell cultures grown submersed in an assay medium containing epidermal growth factor and "2% Matrigel."[5] Appx0234. The cells themselves are grown on "a gelled bed of basement membrane measuring approximately 1 mm in thickness." Appx0234.

[5] "Matrigel remains liquid on ice but solidifies rapidly when warmed . . . ." Appx0235.



Appx0234.

Kirk is a two-page "quick guide" about the volvox algae. Appx0333. The sole image in Kirk is shown as follows:



Id. Kirk does not disclose any schematic or diagram of a volvox, *see* Appx0333–0334, but, according to the examiner, the document teaches

that volvox "is a spherical multicellular green alga containing many small biflagellate somatic cells and non-motile gonida, and moves by a rolling motion," Appx0949. Kirk states that the volvox cells "deposit[] large quantities of a glycoprotein-based extracellular matrix." Appx0333.

The examiner rejected the claims as anticipated by, or in the alternative, obvious over each of the same three preceding references. Appx0956–0958. No separate obviousness analysis was provided. *Id.* The examiner's anticipation analysis of these three references was essentially a verbatim copy of the rejections under § 101.[6]

The examiner also repeated the position that the claims were nonenabled because the "artificial gland" "is structurally dissimilar from a naturally occurring gland in that the structure lacks the mechanism for either constitutive release or regulated release." Appx0951. Thus, despite the examiner's conclusion that the claims read on the prior art mammary gland disclosed in Debnath, the examiner relied on the

[6] Anticipation/obviousness rejections were also based on two separate references, and a separate obviousness rejection was also made. Appx0958–0960.

"dissimilarity" between the claimed "artificial gland" and a naturally occurring gland as a basis for the alleged non-enablement. *Id.*

The rejection also asserted that "the cells comprising the claimed structure certainly would pose a disadvantage" due to possible immunogenicity concerns, although no references were cited in support. Appx0952–0953. The examiner concluded: "Therefore, the claimed structure is not enabled at the time of filing, because the structure is not a gland in the meaning of the art." Appx0953.

Marquez filed a detailed, 36-page response and amendment, attempting to overcome each of the rejections. Appx0909. The primary claim amendment, to claim 1, was offered "in the interest of reaching allowed subject matter." Appx0923. Marquez amended claim 1 as follows:

> An artificial gland ~~that is~~ comprising an independent unit for promoting biological activity, the independent unit consisting of an isolated product, the artificial gland further comprising . . . .

Appx0910. Marquez explained that the amendment "specifies that the claim is to an independent unit that is an isolated product, which necessarily distinguishes it over the in-vivo blastocyst and other naturally occurring glands." Appx0924.

4. The fourth and final office action maintained the rejections and added a written description rejection

The examiner found the arguments and amendments unpersuasive and issued a fourth office action rejecting all the claims. Appx0877–0908.[7] The office action advance many of the same points recited in previous office actions. For example, the examiner contended that "[t]he reasonable breakdown of the term 'artificial gland' is 'a gland made by an artificial method" and therefore "[t]he gland is not artificial." Appx0881.

The examiner continued to focus on possible health and safety risks associated with using the claimed Celloidosomes®, such as a possible "destructive immune response." Appx0896. At one point, the examiner contended that "the living cells composing the artificial micro-gland require feeding" and that "[i]t is not evident that the implanted gland would receive sufficient oxygen and nutrient supplies so that they would survive." Appx0898.

The examiner added a rejection for lack of written description based on amended claim 1. Appx0884–0886. The examiner interpreted the claim amendment as encompassing "something else." Appx0884. In the

[7] Certain rejections, not at issue here, were withdrawn. Appx0879.

examiner's view, "[t]he disclosure indicates the artificial gland is an independent unit and an isolated product, not that the artificial gland is made up of an independent unit and something else, where the independent unit consists of an isolated product, the product being undefined." Appx0884–0885. The examiner so concluded, even though Marquez explained that the term "comprising" had been relocated within the claim "so that [the] requirement of an 'independent unit' and the added limitation are actually interpreted as limiting." Appx0924.

5. The Board affirmed certain rejections such that no claim was deemed patentable

On appeal to the Board, Marquez and the examiner filed their respective briefs, urging many of the same arguments presented during prosecution. Appx0688–0873. For example, the examiner asserted that "[t]o refer to the claimed structure as 'an artificial gland' is misleading and repugnant to the art recognized meaning to the term." Appx0795.

The Board affirmed some rejections but reversed others. Appx0049–0050. With the § 101 rejection, the Board affirmed the rejection of claims 1–4, 7, and 35 and reversed the rejection of claims 33, 34, and 36. The Board held that claim 1 "reads on natural products, specifically the mouse blastocysts described in Zetter and the volvox

algae described in Kirk." Appx0014. The Board disagreed with the § 101 rejection based on Debnath because the "acini-like spheroids" disclosed in Debnath "are not naturally occurring, but rather grown in three-dimensional culture in vitro." Appx0014.

With the anticipation rejections, the Board found that Zetter and Debnath anticipated claims 1, 2, 4, and 7 and but not claims 33 and 34. Appx0033–0042. The Board did "agree that claim 1 may be patentable over Zetter if the method of production in the claim in fact results in structural differences," but it found the evidence of such differences not "persuasive." Appx0036.

The Board also affirmed the anticipation rejection based on Kirk for claims 1, 2, 4, 7, and 35 and reversed for claims 33, 34, and 36. The Board reversed all the anticipation rejections based on Napolitano. Appx0047–0049. The Board presented no independent analysis of the obviousness of any claims based on Kirk, Debnath, Napolitano, and Zetter. Appx0039–0050.

With the enablement rejections, the Board held that claims 33 and 34 fail to satisfy the enablement requirement because the specification "does not provide guidance for the formation of an artificial gland that

contains a membrane of cellular components" or how such a gland may be used "for drug testing, tumor biology and organ/tissue regeneration or replacement." Appx0030. The Board summarily affirmed the enablement rejections of claims 1–5, 7, 8, 13, 31, 32, 35, and 36 because the Board concluded that Marquez did not address those rejections in its opening brief. Appx0029. The Board also concluded that the specification failed to disclose a substantial and specific utility for those claims. Appx0032.

Finally, the Board affirmed the rejection of claims 1–5, 7, 8, and 13 for inadequate written description. Appx0022. The Board adopted the examiner's construction of the terms "comprising," "independent unit," and "isolated product" in the context of the amendment. Appx0022. Like the examiner, the Board understood that the specification "only describes an artificial gland that is an independent unit and an isolated product," Appx0021, but the Board did not give effect to Marquez's express explanation of the amendment. *See* Appx0924.

This appeal follows.

SUMMARY OF THE ARGUMENT

The Board's affirmance of the rejections should be reversed because the decision is legally erroneous and not based on substantial evidence.

First, the Board erred in construing key claim terms, and the erroneous constructions infected the Board's analysis of the claim rejections. The Board adopted claim constructions that are unreasonably broad and divorced from the written description and prosecution history. The Board's interpretation of the following terms should be reversed: "artificial gland," "assembled in . . . a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer," and "bio-reactor."

Second, the claimed invention is patent-eligible under § 101. Contrary to the Board's conclusions, the claim invention is not a product of nature, and the claims do not read on the prior art, naturally occurring glands and organisms. Instead, the Celloidosomes®, assembled with electrostatic and hydrophobic forces, exhibit marked differences from naturally occurring groups of cells grown from a single cell.

Third, the claims are novel under § 102. No cited prior art discloses an "artificial" gland that is "assembled" from individual cells and that is

an "isolated product" and "independent unit" containing a "bioreactor." For this reason, the rejection of claims 1, 2, 4, 7, and 35 as anticipated under 35 U.S.C. § 102 is not supported by substantial evidence and should be reversed.

Fourth, the Board's obviousness ruling is erroneous. The Board did not provide any reasoning or analysis for its § 103 holding. This alone is sufficient for reversal. At best, the Board's obviousness holding is predicated entirely on its anticipation findings, and therefore the obvious rulings should be reversed for the same reasons as stated for the anticipation rejections.

Fifth, in accordance with § 112, the specification enables one of ordinary skill in the art to make and use the claimed invention. Contrary to the Board's view, the application discloses at least one substantial and specific utility of the claimed Celloidosomes®. The application also enables a skilled artisan to make and use the claimed Celloidosomes® without undue experimentation. Neither the Board nor the examiner analyzed the *Wands* factors. Nonetheless, when properly considered, the evidence demonstrates enablement. Thus, the rejection of claims 1–5, 7, 8, 13, and 31–36 should be reversed, or at a minimum vacated.

Sixth, the application adequately describes the claimed invention under § 112. The Board's analysis rests on an erroneous interpretation of the phrase "the independent unit consisting of an isolated product, the artificial gland further comprising." The Board's finding that claims 1–5, 7, 8, and 13 lack written description is therefore not supported by substantial evidence and should be reversed.

ARGUMENT

I. Standards Of Review

This Court reviews the Board's factual determinations for substantial evidence and its legal determinations de novo. *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1073 (Fed. Cir. 2015).

Claim construction is a question of law. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). When the intrinsic record dictates the proper construction of a term, the Court reviews the Board's construction without deference. *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1278 (Fed. Cir. 2017).

Whether a claim is directed to patent-eligible subject matter is reviewed de novo. *In re Nuijten*, 500 F.3d 1346, 1352 (Fed. Cir. 2007).

Anticipation is a question of fact, reviewed for substantial evidence. *In re Hyatt*, 211 F.3d 1367, 1371–72 (Fed. Cir. 2000). Obviousness is a question of law based on subsidiary findings of fact. *Belden*, 805 F.3d at 1073.

Enablement is a legal question, reviewed de novo, and premised on factual underpinnings that are reviewed for substantial evidence. *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1297 (Fed. Cir. 2015). Whether a patent application satisfies the utility requirement, as part of the enablement requirement of § 112, is a question of fact, reviewed for substantial evidence. *In re Ziegler*, 992 F.2d 1197, 1200 (Fed. Cir. 1993). Written description is a question of fact reviewed for substantial evidence. *ULF Bamberg v. Dalvey*, 815 F.3d 793, 797 (Fed. Cir. 2016).

II. The Board Misconstrued Critical Claim Terms

A pervasive error in the Board's ruling is its erroneous construction of key claim terms. The Board employs the broadest reasonable interpretation, but such an interpretation cannot be divorced from the specification and the prosecution history, thus becoming unreasonable. *In re Skvorecz*, 580 F.3d 1262, 1267 (Fed. Cir. 2009) ("The protocol of

giving claims their broadest reasonable interpretation . . . does not include giving claims a legally incorrect interpretation.").

A. The Term "Artificial" Necessarily Excludes Naturally Occurring Organisms and Glands

All claims require the Celloidosomes® to be artificial, *i.e.*, an "artificial gland." The PTO's claim construction ignores this limitation, discounts the specification and prosecution history, and is unreasonably broad.

The term "artificial" necessarily defines a class of things that are man-made and physically different than a naturally occurring substance. The dictionary definition of "artificial" confirms this reading. *See* Merriam-Webster.com, at https://www.merriam-webster.com/dictionary/artificial ("humanly contrived . . . often on a natural model :man-made an artificial limb artificial diamonds").

The term's usage in the technical literature reflects the dictionary definition. Examples abound in the record. *See* Appx0263 ("artificial anisotropic shells"); Appx0267 ("artificial multicellular organisms); Appx0271 ("artificial multicellular structures); Appx0278 ("artificial tissues"); Appx0282 ("artificial microenvironments"); Appx0295 ("artificial organs"); Appx0310 ("artificial tissues"); Appx0334 ("bacterial

artificial chromosome"); Appx0347 ("artificial vascular tree"); Appx0432 ("artificial cell"); Appx442 ("bioartificial pancreas"); Appx0485 ("bioartificial organ research"); Appx0526 ("yeast shells with an artificial mineral shell"); Appx0538 ("bioartificial pancreas"); Appx0581 ("artificial skin"). These usages illustrate acceptance in the art that the term "artificial" excludes anything that is naturally occurring and not man-made.

The "assembled" limitation adds to the non-natural characteristics of the claimed Celloidosomes®. The specification teaches that the artificial glands are assembled from individual cells. Appx0089. A cell-based microstructure that is "assembled" necessarily excludes—and is structurally different from—a biological structure grown from individual cells or occurring in nature.

The correct understanding of "assembled" also flows from the specification, which teaches that "[t]he self-assembly of cells at the liquid/liquid interface is driven by the minimization of the interfacial energy and is enhanced by electrostatic interaction. Appx0110; *see also* Appx0031 (Board noting the "interfacial energy and electrostatic interaction"). Marquez taught that the "artificial" "assembled"

Celloidosomes® "provide[] a new ability to control and arrange subcellular and cell-like structures." Appx0085. That control is not possible with naturally occurring glands (or with prior art colloidosomes).

The requirement that the "artificial gland" be "an independent unit" and "an isolated product" reinforces the "artificial" nature of the claimed subject matter. As Marquez explained during prosecution, these limitations "specif[y] that the claim is to an independent unit that is an isolated product, which necessarily distinguishes it over the in-vivo blastocyst and other naturally occurring glands." Appx0924.

B. The Board Incorrectly Disregarded The Limitation Requiring "a Component Selected from the Group Consisting of a Flow Chamber, a Microfluidic Device, and an Ink Jet Printer"

Claim 1 requires that the cells are "assembled in three dimensions in a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer." The Board erroneously disregarded this limitation, which imparts physically distinguishing characteristics on the claimed cell-based assemblies.

First, under the correct construction, the claimed subject matter must contain a flow chamber, a microfluidic device, and an ink jet printer.

This is a physical limitation of the claimed invention and is supported by the specification. *See* Appx0168.

Second, even if this limitation were not required as a physical component of the claimed invention, the requirement that the artificial gland is "assembled" in a flow chamber, a microfluidic device, or an ink jet printer imparts structural meaning to the claimed Celloidosomes®. Because the cell-based structures of claim 1 are assembled from individual cells, the functional characteristics of the resulting Celloidosomes® necessarily differ from an organically grown cell-based structure. In the claimed invention, the cells are "assembled" through "interfacial energy and electrostatic interaction." Appx0103; Appx0110. The inventors' later publications also described the physical interaction. *See* Appx0201 ("We demonstrated the ability to produce high-quality, monolayer-shelled yeastosome structures under proper conditions when sufficient electrostatic driving forces are present.").

In contrast, cellular structures grown from a single cell, such as the prior art examples cited in the anticipation rejections, necessarily contain a complex extracellular matrix. As explained above, naturally-grown cellular structures require complex extracellular matrices. "Cells grown

in tissue culture flasks interact with the protein molecules adsorbed to the rigid flask surface." Appx0187. "Many microbes in their natural habitats are found in biofilm ecosystems," and "[c]ells in these biofilms are embedded within a matrix of extracellular polymeric material." Appx0256; *see also* Appx0187 (describing the extracellular matrix for endothelial cells).

Marquez's claims covering an "artificial gland" that is "assembled" in a flow chamber, a microfluidic device, or an ink jet printer must exclude natural cell structures lacking those limitations or grown outside of those devices. The Board has not pointed to any evidence indicating that the cited naturally occurring cells and organisms can be grown in a flow chamber, a microfluidic device, or an ink jet printer and create an artificial gland having a bioreactor. In sum, the Board's claim construction erroneously disregarded the limitation requiring "a flow chamber, a microfluidic device, or an ink jet printer."

C. The Board Failed to Properly Construe "Bioreactor"

The Board also failed to reasonably construe the term "bioreactor." *See* Appx0016. The claim term identifies a specific, artificial construct,

and does not encompass any naturally occurring volume created by naturally grown cells.

The term "bioreactor" is a term of art. During prosecution, Marquez explained that the term "bioreactor" means a specific artificial construct. Appx0924. Marquez expressly stated that "[a] bioreactor may refer to any manufactured or engineered device or system that supports a biologically active environment." Appx0924. This definition should control. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc) ("In such cases, the inventor's lexicography governs.").

Marquez's express definition comports with the term's usage in the art. The prior art reported that artificially created volumes within a membrane construct can act as "bioreactors," "microreactors," and "biological microreactors." *See* Appx0228; Appx0268; Appx0588. For example, a 2004 article titled "A Vesicle Bioreactor as a Step Toward an Artificial Cell Assembly" discloses "[a]n *Escherichia coli* cell-free expression system [that] is encapsulated in a phospholipid vesicle to build a cell-like bioreactor." A0432. All usages of the term refer to artificial constructs, and not a single example used the term "bioreactor"

(or similar terms such as "microreactor" or "biological microreactor") to include a naturally occurring volume of a living cell or living organism.

The examiner and the Board acknowledged Marquez's express definition during prosecution but declined to apply it. The examiner insisted that a bioreactor is broad enough to include salivary glands, the pancreas, the pituitary gland, and the thyroid. Appx 0882. "Each of these glands," according to the examiner, "can be considered as bioreactors because they produce proteins that can be isolated in quantity from them." Appx0082. Going further, the examiner pointed to "bovine and porcine pancreas" and concluded that, "[w]hile the animals may not have been called bioreactors, they in essence were bioreactors." Appx0882.

No evidence supports the PTO's reading of "bioreactor" as encompassing "bovine and porcine pancreas." Nor is there any evidentiary basis to conclude that a bioreactor includes entire animals. Such an interpretation is indeed broad but unreasonable. *Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015). ("A construction that is 'unreasonably broad' and which does not 'reasonably

reflect the plain language and disclosure' will not pass muster." (quoting *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010))).

The examiner also applied the erroneous interpretation of bioreactor in the Examiner's Answer brief. Appx0787–0829. The Examiner's Answer neither acknowledges the express definition of "bioreactor" nor addresses how the term is used in the scientific literature. *Id.* The Board's opinion necessarily adopted the examiner's overly broad usage of the claim term.

The PTO's interpretation of "bioreactor" also would encompass embodiments that the specification does not teach how to make. The specification describes specific methods used to assemble the individual cells into a membrane surrounding a liquid, gas, or gel that forms the bioreactor. *See, e.g.*, Appx0097–0101. In those methods, there is no indication that the cytoplasm (or blastocoel) of naturally occurring cells could be used as a bioreactor. The PTO's broad understanding of "bioreactor" is one that "should be viewed with extreme skepticism." *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1376 (Fed. Cir. 2002), *vacated and remanded on other grounds*, 537 U.S. 802 (2002).

In all, the Board and the examiner failed to correctly construe the term "bioreactor," which is a critical limitation of the claims. The unreasonably broad interpretation applied by the PTO adversely affected the Board's analysis of the claim rejections, as discussed below.

III. Claims 31 And 35 Are Directed To Patent-Eligible Subject Matter

Section 101 defines patent-eligible subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. While "this provision contains an important implicit exception," such as "[l]aws of nature, natural phenomena, and abstract ideas," *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293 (2012), "[t]he subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts,'" *Diamond v. Chakrabarty*, 447 U.S. 303, 315 (1980).

The *Chakrabarty* Court held that inventions having "markedly different characteristics from any found in nature and one having the potential for significant utility" are patent-eligible. *Id.* at 310; *see also In re Roslin Inst. (Edinburgh)*, 750 F.3d 1333, 1336 (Fed. Cir. 2014).

Here, the Board affirmed the rejections of claims 1–4, 7, and 35 under § 101 and reversed the rejections of claims 33, 34, and 35. The Board's affirmance is legally erroneous and not supported by substantial evidence.

A. Claim 1

As discussed above, claim 1 requires "a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer." Appx0057. When properly construed, the claim is directed to an "artificial gland," *i.e.*, Celloidosomes®, assembled and contained within a flow chamber, a microfluidic device, or an ink jet printer. These components are physical devices, not products of nature. The Board did not identify any prior art disclosing artificial glands constructed in a flow chamber, a microfluidic device, or an ink jet printer.

Claim 1 also expressly limits the claimed subject matter to "artificial" constructs. That the claimed cellular construct must be artificial necessarily, per the correct claim construction, excludes it from the realm of "products of nature." A person of ordinary skill in the art would know that the claimed "artificial glands" are structurally different than, and therefore exclude, anything that occurs in nature. Section 101

seeks to prevent the tying up of compositions of matter existing in nature, without human inventive activity. *See Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117–18 (2013). That concern is not present here.

The claimed Celloidosomes® also exhibit "markedly different characteristics from any found in nature." *See Chakrabarty*, 447 U.S. at 310. The claimed subject matter covers artificial cell-based constructs that are "assembled" as "isolated" and "independent" units. Appx0057. The structure and composition are unlike anything found in nature, and the claim is patent-eligible because it is "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter." *Chakrabarty*, 447 U.S. at 315.

The claimed artificial glands are assembled in specific devices by employing electrostatic forces and energy minimization, as explained in the claim construction and anticipation sections herein. Indeed, "[m]ost microscale self-assembly approaches use hydrophilic-hydrophobic interactions to assemble subunits." Appx278. Using those interactions, as the inventors did here, creates a microstructure that is structurally and functionally different than a naturally occurring gland or organism.

The "artificial gland" is "assembled" using the specific forces without using a complex extracellular matrix. *See, e.g.*, Appx0284 (explaining that "[t]he molecular constituents of the ECM bind specifically to cells"). It is therefore both an "independent unit" and an "isolated product."

The Board's analysis also runs counter to PTO guidance, which warns that "[c]are should be taken not to overly extend the markedly different characteristics analysis to products that when viewed as a whole are not nature-based." 2014 Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74,618, 74,623 (Dec. 16, 2014). "To show a marked difference, a characteristic must be changed as compared to nature, and cannot be an inherent or innate characteristic of the naturally occurring counterpart." *Id.* (citing *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). Here, the claimed artificial Celloidosomes® exhibit "markedly different" interactions between the cells of the claimed artificial gland, compared to the cited natural products. Nor do naturally occurring products contain a "bioreactor."

The Board identified no evidence demonstrating the claimed artificial glands to exhibit the same properties and features as naturally occurring glands. In fact, the examiner understood that the claimed

structure "is structurally dissimilar from a naturally occurring gland in that the structure lacks the mechanism for either constitutive release or regulated release." Appx0795.

Myriad and *Roslin* are not to the contrary. In *Myriad*, isolated, naturally occurring human DNA sequences were not patent-eligible because they were indistinguishable from products of nature. 133 S. Ct. at 2118. The claimed DNA sequences were identical to what previously existed in nature. *Id.* at 2116 ("It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes.").

Another problem in *Myriad* was that the claims were "concerned primarily with the information contained in the genetic sequence, not with the specific chemical composition of a particular molecule." 133 S. Ct. at 2118. That is not so with Marquez's claims, where there is no danger of patent protection monopolizing information existing in a naturally occurring biological construct.

Similarly, *Roslin* does not support the Board's ruling. In *Roslin*, this Court held that Dolly, a genetic clone of a naturally occurring sheep, was not patent-eligible. 750 F.3d at 1339. The Court explained that

"Roslin's claimed clones are exact genetic copies," and thus there were no meaningful differences between the natural sheep and its clone. *Id.* at 1337.

Unlike in *Roslin*, the claimed "artificial glands" are readily distinguishable from naturally occurring glands. They are, by definition, not naturally occurring, and they are structurally and functionally different from living cellular structures. The claimed Colloidosomes® lack an extracellular matrix and are assembled using electrostatic forces.

The "bioreactor" limitation further confirms the patent-eligibility of claim 1. *See* § IV.A.2, *supra*. As discussed above, "bioreactor" refers to a specific artificial construct. This limitation does not occur in nature and is not disclosed in any prior art reference cited as anticipating the claimed invention.

Finally, the PTO's § 101 rejections are also internally inconsistent. The PTO agrees that claim 31 is patent-eligible but that claim 1 is not. Appx0004. Claim 31 is directed to a similar artificial gland, except the gland is constructed of "biological units." Appx0076. According to the specification, "[b]iological units include fungi, algae, spores, pollen, yeast,

bacteria, and viruses." Appx0095. Claim 31, like claim 1, covers specific novel constructs composed of subunits that exist in nature.

It is not possible to reasonably reconcile the PTO's position that claim 31 is patent-eligible but claim 1 is not. Both are directed to specific, novel microstructures using the building blocks of nature, similar to creating a novel protein using naturally occurring amino acid building blocks. For this reason, the field is referred to as "synthetic biology," Appx0212, or, as one article termed it, "micro-masonry." Appx0278.

Accordingly, claim 1—just like claim 31—is directed to patent-eligible subject matter. The Board's holding should be reversed.[8]

B. Claim 35

The Board affirmed the rejection of claim 35 on the sole basis that "volvox, an algae that occurs in nature, anticipates claim 35, as further discussed below in connection with the rejection of claim 35 under 35 U.S.C. § 102 as anticipated by Kirk."

The Board's entire analysis of claim 35 reads as follows:

> Appellants argue that claim 35 is not directed towards a product of nature because no naturally occurring product anticipates or renders obvious the artificial gland recited in

[8] Claims 1–4 and 7 were argued together, and therefore the Board's ruling for each of those claims should be reversed.

> claim 35. (Appeal Br. 30.) We are not persuaded because we find that volvox, an algae that occurs in nature, anticipates claim 35, as further discussed below in connection with the rejection of claim 35 under 35 U.S.C. § 102 as anticipated by Kirk.

Appx0018. Thus, the Board's 101 analysis of claim 35 is nothing more than an anticipation rejection, and it should be reversed for the reasons stated below. *See* § IV.A, *infra*.

Second, the subject matter of claim 35 is patent-eligible for some of the same reasons set forth above for claim 1. Claim 35 is similar to claim 1, except that claim 35 lacks the limitation of "a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer." Appx0078. Thus, the other limitations, such as "artificial," "assembled," and "bioreactor," apply equally to claim 35, and those limitations establish the patent-eligibility of the claimed subject matter.

IV. The Claimed Artificial Glands Are Novel

The Board affirmed the rejections of claims 1, 2, 4, 7, and 35 as anticipated under § 102. The Board's ruling is not supported by substantial evidence and should be reversed.

A. Several Limitations are Absent from the Cited Prior Art

"A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior

art reference." *In re Paulsen*, 30 F.3d 1475, 1478–79 (Fed. Cir. 1994). Here, the cited prior art does not disclose several claim limitations.

1. "Artificial gland" that is "assembled" from individual cells

Under the correct claim construction, a person of ordinary skill in the art would not consider the cell-based structures of the cited prior art to be "artificial glands," "assembled" from individual cells, forming an "independent unit" and "isolated product." The anticipation rejections of claims 1, 2, 4, 7, and 35 lack substantial evidence support.

The Board disregarded one limitation that defines what is claimed. Applicant claims an "artificial" gland and not a "gland" or a "natural" gland. Applicant respectfully submits that the law does not permit the Board to simply ignore what is claimed and equate it to something not claimed. Such disregard for "each and every limitation" in a claim unbridles the law of anticipation from that which is claimed to that which the reviewing agency arbitrarily deems to be claimed.

The Board also did not account for the requirement that the claims are "assembled" in a "a microfluidic device," or "an ink jet printer." This requirement is more than a mere product-by-process limitation, as the Board suggested. *See* Appx0013. Instead, this limitation imparts

substantial physical characteristics on the claimed Celloidosomes® that differentiate Marquez's artificial constructs from any naturally occurring collection of cells. These limitations have physical consequences to the end product that make the artificial gland a "product of human ingenuity" and not merely "nature's handiwork." *Roslin*, 750 F.3d at 1335–36.

Significant physical differences exist between the claimed artificial assembly of cells and the cited naturally grown cell-based organisms and glands. As the specification explains, and as the Board recognized, the claimed Celloidosomes® are constructed using electrostatic and energy minimization forces. Appx0031. Naturally occurring glands and cell growths are not held together using "electrostatic forces," and the PTO has never contended that they are.

Moreover, naturally grown cells and glands contain a complex extracellular matrix, *see, e.g.*, Appx0256, which is not part of the claimed "assembled" and "isolated" "artificial gland." For example, Kirk describes the volvox colony as having its cells embedded in an "extracellular matrix." Appx0333. Zetter provided fluorescent photomicroscopy images of LETS proteins on the blastocysts and that the "LETS protein is found

on the surface of these cells and is frequently concentrated in the areas of intercellular contacts." Appx0592.

The cells used to manufacture a membrane in accordance with the present invention are necessarily free standing cells. The cells must be separately manipulable, as opposed to embedded in an extracellular matrix, so that they can be assembled into a membrane within in "a flow chamber, a microfluidic device, [or] an ink jet printer." *See, e.g.*, Appx0168, Fig. 7. This physical characteristic is a necessary feature of the claimed invention that results from the physical manipulation of the cells into the claimed "artificial gland."

In sum, Zetter's blastocysts and Kirk's volvox are the end product of cells natural growth and are not not an assembled structure of individual cells, configured in specific machinery using electrostatic and hydrophobic-hydrophilic forces. The blastocysts and volvox are not "an independent unit and isolated product," as required by the claim. The Board failed to recognize these structural and functional differences that necessarily flow from the method of assembling the "artificial gland."

2. Bioreactor

Each cited reference also does not disclose a "bioreactor." Applying the correct claim construction, *see* § II.C, *supra*, the naturally occurring cell-based structures do not contain a bioreactor.

As explained above, a bioreactor is a term of art referring to an artificially created volume that can be used to perform specific functions. A bioreactor does not include naturally occurring cytoplasmic space, and the PTO has not identified a single reference using the term "bioreactor" to include a naturally occurring cytoplasmic volume.

Each cited prior art reference discloses only a volume created by the natural growth of cells. Zetter discloses a drawing of a mouse blastocyst. The blastocyst contains a fluid-filled cavity called a blastocoel, but the blastocoel cannot be considered a "bioreactor" as that term is used in the art. Appx0591. Kirk's two-page "quick guide" did not disclose a bioreactor. Appx0333. Debnath described cultured "mammary epithelial acini" but no bioreactor. Appx0234.

None disclose an assembled cell construct having an artificial interior volume that acts as a "bioreactor." The bioreactor of the claimed invention forms from the liquid, gas, or gel that is used in the process of

assembling the Celloidosomes® from individual cells or cellular components. *See, e.g.*, Appx0097–0101. Further, none of the references discloses that the interior volumes contain "a product of activity of the cells," which the "bioreactor" does have as required by the claims.

The Board's affirmance of the rejection of claims 1, 2, 4, 7, and 35 is not supported by substantial evidence.

3. Component Physicality

Claim 1 further requires "a flow chamber," "a microfluidic device," or "an ink jet printer." As explained above, the proper claim construction recognizes this limitation as a physical component of the claimed invention. *See* § IV.A.3, *supra*. There is no dispute that the three cited references do not disclose any one of these physical components. The PTO has never claimed otherwise. Furthermore, as explained above, the process of assembling the artificial gland, using electrostatic forces, in "a flow chamber," "a microfluidic device," or "an ink jet printer" necessarily creates an artificial cell-based construct that differs from anything shown in the prior art references. Accordingly, the anticipation rejection of claims 1, 2, 4, and 7 is not supported by substantial evidence.

* * *

The three prior art references do not disclose "each and every limitation" because no prior art reference discloses an "artificial gland" that is "assembled" from individual cells as an "independent" and "isolated" structure and that contains a "bioreactor." Furthermore, no prior art reference teaches the device limitation requiring "a flow chamber," "a microfluidic device," or "an ink jet printer." The Board's affirmance of the anticipation rejection of claims 1, 2, 4, 7, and 35 is therefore not supported by substantial evidence.

V. The Board Provided No Factual Findings Or Reasoning For Its Obviousness Ruling, Which Must Be Reversed

Obviousness is a question of law predicated on subsidiary fact findings. *Belden*, 805 F.3d at 1073. Whether a person of ordinary skill in the art would have been motivated to modify or combine prior art is a question of fact. *Id.* "[O]bviousness findings grounded in common sense must contain explicit and clear reasoning providing some rational underpinning why common sense compels a finding of obviousness." *In re Van Os*, 844 F.3d 1359, 1361 (Fed. Cir. 2017) (quotations omitted).

Here, the Board's obviousness conclusions cannot be affirmed for two reasons. First, the Board gave no reasoning or explanation for affirming the obviousness rejections. While "anticipation is the epitome

of obviousness," *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983), that maxim does not relieve the agency of establishing a reasoned basis for its statutory obviousness rejection. If the PTO deems the claims obvious, the PTO must offer the necessary factual findings and legal analysis under *Graham v. John Deere Co.*, 383 U.S. 1 (1966). *See In re Lee*, 277 F.3d 1338, 1342 (Fed. Cir. 2002) (noting "the obligation of the agency to make the necessary findings and to provide an administrative record showing the evidence on which the findings are based, accompanied by the agency's reasoning in reaching its conclusions").

Second, the Board's obviousness holding rests solely on its conclusion that the claims are anticipated under § 102. To the extent the Board can be deemed to have provided a sufficient obviousness analyses, they are entirely duplicative of its anticipation findings. Accordingly, the Board's obviousness rulings should be reversed for the same reasons as noted above for the anticipation rejections.

VI. Claims 1–5, 7, 8, 13, And 31–36 Are Enabled And Provide A Specific And Substantial Utility Under § 112

The Board affirmed the rejection of claims 1–5, 7, 8, 13, and 31–36 under § 112 (enablement) on two distinct grounds. First, the Board held

that undue experimentation would be required to make and use the invention. Second, the Board held that the specification failed to disclose a specific and substantial utility of the claimed artificial glands. Neither holding is legally correct, and neither is supported by substantial evidence.

A. The Application Discloses Specific and Substantial Utilities

A patent application must disclose a "specific" and "substantial" utility for the claimed invention. *Brenner v. Manson*, 383 U.S. 519, 534–35 (1966); *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005). A "substantial" utility is analogous to "practical" utility, or "real world" utility. *Fisher*, 421 F.3d at 1371. The "specific" utility requirement mandates that "an application must disclose a use which is not so vague as to be meaningless." *Id.*

"[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762 (Fed. Cir. 1984). Importantly, "[w]hen a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown." *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958 (Fed. Cir. 1983).

Here, the PTO bears the burden for establishing a lack of utility. *In re Cortright*, 165 F.3d 1353, 1357 (Fed. Cir. 1999). "The PTO may establish a reason to doubt an invention's asserted utility when the written description 'suggest[s] an inherently unbelievable undertaking or involve[s] implausible scientific principles.'" *Id.* (quoting *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995)).

Here, the PTO failed to meet its burden because Marquez disclosed at least one substantial and specific utility of the claimed artificial gland constructs.[9] The application teaches that the artificial gland constructs can "support the growth of organs and other biological material without the use of macro-scale scaffolds." Appx0084. The claimed constructs can also "control the 3-dimensional arrangements of cells and subcellular systems in such a way that can mimic nature." *Id.* The characteristics of the claimed invention thus "has application to three-dimensional (3-D) *in vitro* cell cultures, in which cells are grown in environments that more

[9] The Board's rejection based on a lack of a specific or substantial utility appears to have been a new ground of rejection by the Board, as the examiner never asserted during prosecution or briefing before the Board that the patent application failed to identify a substantial and specific utility, as required under § 101 (and § 112). *See* Appx0793–0797; Appx0812–0815; Appx0830–0873.

closely mimic native tissue architecture and function." Appx0086. These are specific and substantial utilities; entire industries and classes of inventions are based on supporting the growth of biological materials and preparing in vitro cell cultures.

Dismissing these specific uses, the Board held that Marquez's "broad statements regarding potential use of the claimed artificial glands (FF17–19) do not describe the 'specific and substantial' utility needed to satisfy the enablement requirement." Appx0032. The Board concluded that uses such as "stem cell engineering" and "biological tissue and organ repair and replacement" are "too vague to provide *specific* utility." Appx0032 (emphasis in original). The Board also contended that the application did not prove that the claimed invention "is 'useful to the public as disclosed in its current form.'" *Id.* (quoting *Fisher*, 421 F.3d at 1371).

The PTO did not satisfy its burden of challenging Marquez's presumptively correct assertion that the claimed Celloidosomes® perform the functions. "[T]he Office must (A) make a *prima facie* showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the

prima facie showing." Manual of Patent Examining Procedure ("MPEP") § 2107.02(IV), at 2100–40 (Nov. 2015); *see also Brana*, 51 F.3d at 1566. Here, the Board cited no evidence to support its conclusion that the asserted utilities are not a "real world" utility.

Second, the Board's conclusion is not supported by Supreme Court or this Court's precedent. In *Brenner v. Manson*, the Supreme Court held that the patent failed to disclose a substantial and specific utility for the claimed method of making specific steroidal compounds because there was no known use for the compounds. 383 U.S. at 534. Unlike in *Brenner*, the Celloidosomes® have numerous known uses, some of which are based on the known uses of the related colloidosomes. The record is replete with such examples. *See, e.g.*, A0392 ("Microencapsulation . . . provides a potential way to overcome the need for immunosuppressive drugs."); Appx0450 (describing "microencapsulation" as a means for pancreas islet transplantation). A 2008 review article highlighted that other examples of similar microstructures "are useful for a variety of applications ranging from microparticle fabrication to vesicle formation, and chemical synthesis to high-throughput screening of single cells." Appx0512.

The present application is also distinguishable from *Fisher*, where this Court held that an application claiming certain expressed sequence tags ("ESTs") did not disclose a substantial and specific utility. 421 F.3d 1379. The applicant did not know of any specific utility for the five claimed EST sequences. *Id.* at 1368 ("Fisher did not know the precise structure or function of either the genes or the proteins encoded for by those genes."). The seven general uses were not sufficient because, as the Court observed, "all of Fisher's asserted uses represent merely hypothetical possibilities, objectives which the claimed ESTs, or any EST for that matter, could *possibly* achieve, but none for which they have been used in the real world." *Id.* at 1374 (emphasis in original). For instance, Fisher asserted that "the claimed ESTs could be used to identify polymorphisms or to isolate promoters" but did not have "any evidence . . . showing that the claimed ESTs have been used in either way." *Id.*

In contrast, Marquez taught that the claimed Celloidosomes® are a "new means for manipulating controlled releases or absorptions supporting biological activity." Appx0086. The Celloidosomes® also "solve[] nagging problems inherent in 3-D cell cultures by providing a uniquely configurable core/shell living micro-capsule or artificial micro-

gland, which delivers a needed ability to control cell architecture in the shell while maintaining the core as an artificial micro-environment." *Id.*

The PTO's analysis overlooks several publications reporting that the claimed Celloidosomes® could be used in "applications as bio-capsules with an inner core storage capability, which would render them useful in the field of tissue engineering." Appx0208. Dr. Cheng's declaration also identified "peered reviewed scientific reports on the manufacture and use of the artificial gland to be supportive of the operability, functionality and usefulness of the claimed artificial gland." Appx0673–0674 (identifying a list of nine publications/presentations). The Board did not address this evidence in its ruling. *See* Appx0032.

Subsequent, independent research confirmed the utility of the claimed Celloidosomes®. The UK research group reported on the utility of Celloidosomes®, explaining that "[s]uch structures may find applications as drug carriers, biological microreactors, and templates for tissue engineering." Appx0268. According to that report, "[c]elloidosomes may be used as a simple model of colonial microorganisms and serve as a starting point for development of artificial symbiotic multicellular organisms." *Id.* These are specific real-world

uses—both in vitro and in vivo—of a novel, artificial construct of assembled cells.

Finally, the PTO's Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001), confirm that Marquez's application discloses a substantial and specific utility. The utility requirement "excludes 'throw-away,' 'insubstantial,' or 'nonspecific' utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement." *Id.* at 1099. Here, Marquez identified at least one specific, substantial utility, for example, as drug carriers, biological microreactors, and templates for tissue engineering. These are not "throw-away" uses intended for the landfill.

The PTO's utility analysis succumbed to error by requiring the specification to establish multiple uses, with an undue emphasis on requiring "constitutive or regulated release." *See* Appx0795. The law is clear, however: "When a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown." *Raytheon*, 724 F.2d at 958. Marquez's application teaches a multiple substantial and specific uses, consistent with patent law's incentive to disclose.

B. The Specification Adequately Enables the Claimed Artificial Gland Constructs

Section 112 requires a patent application to enable "those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation.'" *Invitrogen Corp. v. Clontech Labs. Inc.*, 429 F.3d 1052, 1070–71 (Fed. Cir. 2005). The factors that must be considered when assessing enablement "include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

The Board's conclusion that the claimed subject matter is not enabled is erroneous and not supported by substantial evidence. First, the Board's enablement analysis rests on the incorrect claim constructions discussed above. For instance, the Board appears to adopt the examiner's flawed interpretation of "gland" as requiring "either constitutive release or regulated release." Appx0023. Accordingly, the Board's conclusions must, at a minimum, be vacated.

Second, for the reasons discussed below, the Board erred in concluding that Marquez waived its arguments regarding the enablement rejections of all but claims 33 and 34. The usual course would be to remand, but the legal question of enablement might be ruled on by the Court because the Board's erroneous reasoning applies equally to all pending claims.

Third, the Board did not conduct a proper analysis pursuant to the *Wands* factors. The Board recited the *Wands* factors, Appx0028, but that was all. Instead of making findings of fact under *Wands* and then analyzing those facts, the Board merely accepted two of the examiner's conclusions: (1) the specification lacks guidance on how the claimed artificial gland "may be used 'for drug testing, tumor biology and organ/tissue regeneration or replacement' as disclosed in the [s]pecification," Appx0030 (quoting Examiner's Answer, Appx0798); and (2) the specification "does not provide guidance for the formation of an artificial gland that contains a membrane of cellular components," *id.* (quoting Examiner's Answer, Appx0798). Neither conclusion is correct.

On the first, the Board provided no analysis of why it believed there was insufficient guidance about how to use the Celloidosomes® "for drug

testing, tumor biology and organ/tissue regeneration or replacement." The Board's decision merely states the conclusion without analysis. *See* Appx0030. This is not a reasoned analysis, as required by law. *Cf. In re Kahn*, 441 F.3d 977, 987 (Fed. Cir. 2006) ("[T]he Board must provide some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct.").

Furthermore, the Board's decision is wrong for at least two reasons. The Board overlooked enabled uses, instead focusing primarily on certain proposed therapeutic uses. Specifically, Marquez taught that the "invention provides new means for manipulating controlled releases or absorptions supporting biological activity." The Board did not address this asserted use in the contact of in vitro use and the technical documents of record confirm the enablement.

Using artificially constructed vesicles to deliver drugs and other biologically actives is well known and the subject of extensive research. One article reported that "[v]arious controlled release systems, such as microemulsions, micelles, liposomes, niosomes and nanoparticles, have been developed over the past few decades." Appx0175. Another report, describing related emulsion technology, reviewed that they are "widely

sued to encapsulate active ingredients in myriad applications, including drug delivery, foods, cosmetics, chemical separations, and syntheses of microspheres and microcapsules." Appx0225. The UK group, which conducted independent research on Celloidosomes®, recognized that the novel structures could "find wide range of practical applications in the development biological microcontainers, tissue engineering of hollow transplants and in other areas of biotechnology." Appx0277.

The Board's approach appears to have repeated the examiner's error during prosecution. There, the examiner focused primarily on issues such as safety and efficacy. But one need not prove with certainty that the invention will meet human safety and efficacy standards for an invention to be enabled. *See Brana*, 51 F.3d at 1568 ("FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws."); *see also* MPEP § 2164.01(c) ("The applicant need not demonstrate that the invention is completely safe.").

Ultimately, an applicant need disclose only one enabled use when claiming a composition of matter. Here, Marquez has done so, and more. The pending claims are enabled under § 112.

The Board also erred in concluding that claims 33 and 34 are not enabled. The specification provides detailed methods of making the Celloidosomes®, with several working examples constructed from whole cells. The specification explains that the same general methods would be used when using cellular components instead of whole cells. The Board cited no evidence to dispute the teaching.

In fact, a person of ordinary skill in the art would reasonably expect the same general process that works with colloidal particles and whole cells to also work with components of a cell. Components of a cell are intermediate in size compared to chemical colloidal particles and whole cells. The same physicochemical forces, *e.g.*, electrostatic, that work for colloidal particles and cells would work with cellular components. The scientific literature explained that "[m]ost microscale self-assembly approaches use hydrophilic-hydrophobic interactions to assemble subunits." Appx0278. More importantly, the Board has not identified any evidentiary basis to question Marquez's teaching of how to make the artificial glands based on cellular components. *See* Appx0031–0032.

In sum, the Board failed to properly analyze the *Wands* factors. The evidence demonstrates that the quantity of experimentation needed

to make and use the claimed Celloidosomes® is low, the specification provides ample, detailed guidance with several working examples, the state of the art is well-developed for creating and using known microcapsules, such as colloidosomes and emulsions, and the level of skill in the field is high. While the claims are broad with some unpredictability in the field, that is not unusual for a breakthrough invention. Weighed as a whole, the factors strongly favor enablement.

C. Marquez Addressed the Enablement Issues Applicable to All Rejected Claims

The Board erroneously concluded that Marquez addressed only claims 33 and 34 in response to the enablement rejection. *See* Appx0029. Marquez's appeal brief to the Board responded to the fundamental basis for the examiner's enablement rejection, and the Board should have affirmed the enablement of all pending claims.

In the final office action, the examiner had rejected claims 1–5, 7, 8, 13, and 31–36 for lacking enablement. Appx0886–0903. The examiner's rejection relied primarily on an erroneous view that the claimed "artificial gland" must exhibit the properties of a naturally occurring gland, such as "controlled or constitutive release." *See* Appx0892. This view was repeated in the Examiner's Answer, where the

examiner stated that "a gland possesses critical structures that enable and facilitate the release of products from the cells of the glands" and that "[t]he present claims are not enabled because it is structurally dissimilar from a naturally occurring gland in that the structure lacks the mechanism for either constitutive release or regulated release." Appx0795. The enablement dispute was, in short, a disagreement about what was meant by the term "gland." *See* Appx0795 ("To refer to the claimed structure as 'an artificial gland' is misleading and repugnant to the art recognized meaning of the term.").

In the opening brief before the Board, Marquez first stated that "[a]ll of the rejections are in error and are discussed below" and that "[a]ll should be reversed for the reasons given." Appx0716. Marquez then proceeded to address the examiner's erroneous view of what was meant by an artificial gland. Appx0719. Marquez also disputed the examiner's attempt "to fit the claimed manufacture into her medical definition of gland." Appx0728. Referring to the examiner's mistaken interpretation of "an artificial gland," Marquez directed the Board to the examiner's enablement rejection, which stated that the claims "are not enabled

because it is structurally dissimilar from a naturally occurring gland." Appx0719 (quoting Appx0951 (enablement rejection)).

Marquez's opening brief further relied on the Rule 1.132 declaration from Dr. Cheng that was submitted during prosecution to respond directly to the enablement rejection. Marquez quoted Dr. Cheng's declaration: "I also take the opportunity to point to peered reviewed scientific reports on the manufacture and use of the artificial gland to be supportive of the operability, functionality and usefulness of the claimed artificial gland." Appx742 (quoting Appx0673). This is further evidence that Marquez was addressing the basic deficiency in the examiner's enablement rejection.

Moreover, the Board had before it all the evidence and argument it needed to rule on the enablement rejection of all pending claims. The examiner set forth the bases for the rejection in the Examiner's Answer, and Marquez responded to those points, consistent with 37 C.F.R. § 41.41(b), in the reply brief. *See* Appx0865–0866. There was no attempt to raise new issues or introduce new evidence for the first time in the reply brief, and the Board should have addressed all enablement

rejections. *See In re Beaver*, 893 F.2d 329, 330 (Fed. Cir. 1989); *In re Nielson*, 816 F.2d 1567, 1571 (Fed. Cir. 1987).

Accordingly, Marquez expressed disagreement with the enablement rejections, the relevant evidence was before the Board, and the Board should have reversed the § 112 enablement rejections.

VII. The Specification Provides A Written Description For The Claimed Artificial Gland As "An Independent Unit" And "An Isolated Product"

The Board affirmed the rejection of claims 1–5, 7, 8, and 13 for failing to satisfy the written description under 35 U.S.C. § 112. The Board's finding is not supported by substantial evidence, and it should be reversed. The Board's affirmance adopts the examiner's unreasonably broad interpretation of the claim language, in particular the term "comprising," which was used to specify that the artificial gland is "an independent unit and an isolated product."

Claim 1 covers an artificial gland "comprising an independent unit for promoting biological activity, the independent unit consisting of an isolated product, the artificial gland further comprising . . . ." Appx0057. The language defines the claimed "artificial gland" to be "an independent unit" and "an isolated product." *See, e.g.*, Appx0924.

This description aligns with the application's specification. Indeed, the examiner understood that the application "indicates the artificial gland is an independent unit and an isolated product." Appx0884. The Board also concluded that the specification "only describes an artificial gland that is an independent unit and an isolated product." Appx0021.

The prosecution history confirms Marquez's construction of the claim. In response to the third office action, Marquez amended claim 1 to further distinguish the claimed artificial gland from the prior art blastocyst and the other naturally occurring cell structures. Marquez amended claim 1 as follows:

> An artificial gland ~~that is~~ comprising an independent unit for promoting biological activity, the independent unit consisting of an isolated product, the artificial gland further comprising . . . .

Appx0910 (additions shown as underlined and deletion shown as strikethrough).

The amendment, as Marquez explained, "specifies that the claim is to an independent unit that is an isolated product, which necessarily distinguishes it over the in-vivo blastocyst and other naturally occurring glands." Appx0925. This is a clear declaration that the claimed artificial gland is described as being simultaneously an "independent unit" and an

"isolated product"—and that it does not cover an independent unit for promoting biological activity and "something else." *Cf. Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1306 (Fed. Cir. 2007) ("To operate as a disclaimer, the statement in the prosecution history must be clear and unambiguous, and constitute a clear disavowal of scope." (citing *Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1356–57 (Fed. Cir. 2004))).

Marquez also explained that the amendment "advances the location of the transitional phase 'comprising' so that requirement of an 'independent unit' and the added limitation [*i.e.*, "isolated product"] are actually interpreted as limiting." Appx0925. In other words, the word "comprising" was moved closer to the beginning of the claim so it was understood that each recited limitation, such as "independent unit" and "isolated product," modified the claimed "artificial gland."

Rather than read the claim language in the context of the specification and the prosecution history, the PTO rigidly interpreted the claims terms without consideration of the specification or the prosecution history. Appx0019–0023. The Board erroneously limited its analysis to an isolated reading of the term "comprising," even though the contextual

use of the term and the clear teaching of the specification established that the term was being used to set forth limiting features of the claimed artificial gland.

The Board's reading of the term "comprising" is not reasonable. *Suitco Surface*, 603 F.3d at 1260 ("The broadest-construction rubric coupled with the term 'comprising' does not give the PTO an unfettered license to interpret claims to embrace anything remotely related to the claimed invention."). The record as a whole shows that Marquez was unambiguously using the term "comprising" in a manner to demarcate limiting features of the claimed subject matter, and not in the conventional manner. Such terms do, of course, have presumptive meanings, *see, e.g.*, *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997), but context will trump the presumptive meanings, especially when the inventors act as their lexicographers, *see, e.g.*, *Phillips*, 415 F.3d at 1320–21.

Here, both Marquez and the PTO agree that the application provides written description support for the claimed artificial gland only as being "an independent unit and an isolated product." Appx0884; Appx0924. Marquez explicitly explained the meaning of the claim

amendment. Appx0924. It is unreasonable for the Board to select a claim construction that overlooks this express definition because that approaches severs the claim text from the application's written description and its prosecution history. *See In re NTP, Inc.*, 654 F.3d 1279, 1288 (Fed. Cir. 2011) (explaining that the Board's construction "cannot be divorced from the specification and the record evidence").

Indeed, the examiner first raised the written description rejection in the last office action, and it highlighted the examiner's disconnected claim interpretation. Appx884–0885. The examiner recognized the specification's clear teaching: "The disclosure indicates the artificial gland is an independent unit and an isolated product . . . ." Appx0884. But the examiner then insisted that the amended claim was broader than the disclosure and captured "something else." Appx0885. The examiner's interpretation is possible only by ignoring the prosecution history and the written description.

The PTO's erroneous claim construction opts for breadth without regard to the prosecution history and the specification. The result is an unreasonable interpretation. With the applicants' explanation of the amendment in the prosecution history, there is no disagreement about

the intended claim scope or what was described in the application. Accordingly, claims 1–5, 7, 8, and 13 are supported by an adequate written description under 35 U.S.C. § 112.

VIII. Conclusion

Based on the foregoing, the claims are directed to patent-eligible subject matter and satisfy the patentability requirements. The Board's decision should be reversed or vacated and remanded.

Date: September 25, 2017

Respectfully submitted,

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ADDENDUM

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MANUEL MARQUEZ,
SAMANTHA M. MARQUEZ, and ANTONIO GARCIA[1]

Appeal 2015-007398
Application 12/726,158
Technology Center 1600

Before JEFFREY N. FREDMAN, TAWEN CHANG, and RYAN H. FLAX, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to an artificial gland, which have been rejected as directed to non-statutory subject matter, lacking in written description, non-enabled, and anticipated or obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Appellants identify the Real Party in Interest as the inventors Manuel Marquez and Samantha Marquez. (Appeal Br. 3.)

STATEMENT OF THE CASE

"Tissue and organ engineering are popular terms used to describe efforts to form complex living structures using cells as building blocks." (Spec. ¶ 3.) According to the Specification, "[m]ore sophisticated tissue structures are presently possible using scaffolding, which requires the use of a macro-scale material that can promote 3-dimensional cell organization into tissue by providing a surface for cell attachment and proliferation." (*Id.* at ¶ 6.) Further according to the Specification, the present invention provides a "micrometer-to-millimeter-scale artificial gland comprising a membrane of cellular material surrounding a reservoir comprising a bioreactor," which is "capable of being used to support the growth of organs and other biological material without the use of macro-scale scaffolds" and "can control the 3-dimensional arrangements of cells and subcellular systems in . . . a way that can mimic nature." (*Id.* at ¶ 18.)

Claims 1–5, 7, 8, 13, and 31–36 are on appeal. Claim 1 is illustrative and reproduced below:

> 1. An artificial gland comprising an independent unit for promoting biological activity, the independent unit consisting of an isolated product, the artificial gland further comprising:
> cells assembled in three dimensions in a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer, the cells organized to form a membrane, the membrane configured to define an enclosed volume; and,
> a reservoir within the enclosed volume, the reservoir comprising a bio-reactor containing a product of activity of the cells.

(Appeal Br. 77 (Claims App'x).)

The Examiner rejects claims 1–4, 7, and 33–36 under 35 U.S.C. § 101 as being directed to non-patentable subject matter.[2] (Ans. 3.)

The Examiner rejects claims 1–5, 7, 8, and 13 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement.[3] (*Id.* at 5.)

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[2] There is some confusion as to which claims are subject to the rejection under 35 U.S.C. § 101. In the June 3, 2014 Office Action, the Examiner stated that "[c]laims ***1–7 and 31–36*** are rejected under 35 U.S.C. [§] 101 because . . . the cells of claims ***1, 2, 4, 7 and 31–36*** do not indicate the 'hand of man.'" (June 3, 2014 Office Action 2 (emphasis added).) In the Final Rejection, the Examiner states that "[c]laims ***1–4, 7, and 34–36*** are rejected under 35 U.S.C. [§] 101 because . . . the cells of claims ***1, 2, 4, 7 and 31–36*** do not indicate the 'hand of man' for reasons set forth in the office action mailed June 3, 2014." (Final Act. 2 (emphasis added).) In the Appeal Brief, Appellants stated that all of the claims, i.e., claims ***1–5, 7, 8, 13, and 31–36***, are rejected under 35 U.S.C. § 101 (Appeal Br. 29). In the Answer, the Examiner did not appear to have included any new ground of rejection or withdrawn the rejection of any claim under 35 U.S.C. § 101, but now states that "[c]laims ***1–4, 7 and 33–36*** remain rejected under 35 U.S.C. [§] 101." (Ans. 3 (emphasis added).) Finally, in the Response to Arguments section of the Answer, the Examiner states both that "[c]laims ***1–4, 7 and 33–36*** remain rejected under 35 U.S.C. [§] 101" and that "claims 31 and 33 are ***not*** rejected under 35 U.S.C. [§] 101." (*Id.* at 15 (emphasis added); *see also id.* at 20 (analyzing claims 33 and 34 under 35 U.S.C. § 101).) Taking all of the above into account, particularly the Examiner's explicit statement that claim 31 is not rejected under 35 U.S.C. § 101, the analysis of claims 33 and 34 under 35 U.S.C. § 101 in the Answer, and the corresponding lack of analysis of claims 31 and 32, we understand for purposes of this decision that the Examiner's 35 U.S.C. § 101 rejection applies to claims 1–4, 7, and 33–36.

[3] Our analysis does not change regardless of whether the Examiner's written description and enablement rejections are based upon 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph.

The Examiner rejects claims 1–5, 7, 8, 13, and 31–36 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement. (*Id.* at 7.)

The Examiner rejects claims 1, 2, 4, 7, 33, and 34 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Zetter.[4] (*Id.* at 13.)

The Examiner rejects claims 1, 2, 4, 7, 33, and 34 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Debnath.[5] (*Id.* at 14.)

The Examiner rejects claims 1, 2, 4, 7, and 33–36 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Kirk,[6] as evidenced by Volvox Study Guide.[7] (*Id.*)

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[4] Bruce R. Zetter et al., *Expression of a high molecular weight cell surface glycoprotein (LETS protein) by preimplantation mouse embryos and teratocarcinoma stem cells*, 75 PROCEEDINGS NAT'L. ACAD. SCI. 2324 (1978).

[5] Jayanta Debnath et al., *Morphogenesis and oncogenesis of MCF-10A mammary epithelial acini grown in three-dimensional basement membrane cultures*, 30 METHODS 256 (2003).

[6] David L. Kirk, Quick Guide, *Volvox*, 14 CURRENT BIOLOGY R599 (2004).

[7] We were unable to locate citation information for the Volvox Study Guide in either the Answer or the Final Rejection. Nevertheless, the Volvox Study Guide is cited only as evidence of the size of the volvox spheroid, which we understand is relevant only to the limitation in claim 3 that "the artificial gland has a dimension not exceeding 500 microns." As Appellants did not separately argue claim 3, the Volvox Study Guide is not necessary to our decision.

The Examiner rejects claims 1, 2, 4, 5, and 33–36 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Napolitano.[8] (*Id.* at 15.)

I.

Issue

The Examiner has rejected claims 1–4, 7, and 33–36 under 35 U.S.C. § 101 as being directed, without significantly more, to a judicial exception to patentable subject matter. The Examiner finds that the claims relate to

> an artificial gland that is an independent unit for promoting biological activity, the artificial gland comprising: cells assembled in three dimensions and organized to form a membrane, the membrane configured to define an enclosed volume; and, a reservoir within the enclosed volume, the reservoir comprising a bio-reactor containing a product of activity of the cells.

(Ans. 3.) The Examiner finds that the remaining limitations of the claims, such as cells being assembled "in a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer," "relates to the method of making the gland" and "are not claimed to be part of the gland." (Final Act. 5.) Thus, the Examiner finds that such limitations do not impact the analysis with respect to 35 U.S.C. § 101. (*Id.*; *see also* Ans. 18.)

Based on the above, the Examiner finds that the artificial gland of the claims reads on "naturally occurring aggregates of cells" such as those

[8] Anthony P. Napolitano et al., *Dynamics of the Self-Assembly of Complex Cellular Aggregates on Micromolded Nonadhesive Hydrogels*, 13 TISSUE ENGINEERING 2087 (2007).

disclosed in Zetter, Debnath, and Kirk. (Ans. 3–4.) In particular, the Examiner finds that Zetter teaches

> a 4-day mouse blastocyst contain[ing] two distinct cell types: an outer layer of trophectoderm that encloses a fluid-filled cavity, the blastocoel, and the pluripotent [inner cell mass] ICM at one end of the blastocoel. As shown, the 4 day blastocyst is about 100 microns. The blastocyst comprises cells forming a membrane around a fluid filled cavity, the blastocoel, containing proteins secreted by the cells, and additional cells, the ICM.

(*Id.* at 4 (citations omitted).) The Examiner also finds that Debnath teaches

> the in vitro formation of mammary gland acini possessing a hollow luminal space surrounded by cells, containing milk protein secretion products from the cells. The acini is about 50 microns in diameter. The mammary gland acini is comprised of mammary epithelial cells surrounding a hollow, which would be air filled, center containing secreted milk proteins and tissue fluid.

(*Id.* (citations omitted).) Finally, the Examiner finds that Kirk teaches that

> volvox is a spherical multicellular green alga containing many small biflagellate somatic cells and non-motile gonidia, and moves by a rolling motion. The volvox spheroid contains within its core extracellular matrix and juvenile spheroids. The volvox spheroid is 350-500 microns in size. Thus, the volvox spheroid is composed of volvox cells that form a membrane surrounding a gel center that contains cells as well as secreted volvox proteins, the extracellular matrix. Volvox meets the limitations of the claims.

(*Id.* at 4–5 (citations omitted).)

Appellants contend that independent claims 31 and 33 do not recite cells and thus the Examiner's rationale with respect to the 35 U.S.C. § 101

rejection is inapplicable as to those and related claims.[9] (*Id.* at 30, 34.) With respect to the remaining claims, Appellants contend that the claims are not directed to natural products (Appeal Br. 29, 31), and that, in any event, the claims as a whole recite something significantly different than a natural product. (*Id.* at 32–38.)

Appellants do not separately argue claims 2–4 and 7. We thus limit our analysis to claims 1 and 33–36. The issue with respect to this rejection is whether the evidence of record supports the Examiner's conclusion that claims 1 and 33–36 are directed to non-patentable subject matter.

Fact

1. Zetter describes that, "[a]t the blastocyst stage (approximately 64 cells) [a mouse] embryo contains two distinct cell types: an outer layer of trophectoderm that encloses a fluid-filled cavity, the blastocoel, and the pluripotent [inner cell mass] ICM at one end of the blastocoel." (Zetter 2325, right column.)

2. Zetter describes flushing the mouse embryos by standard procedures from the oviduct or the uterus of a mouse. (Zetter 2324, right column.)

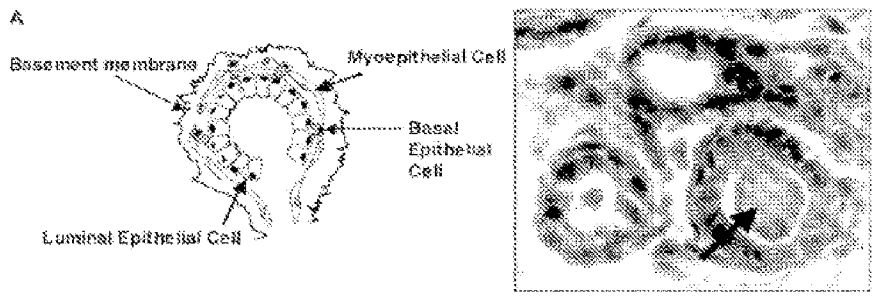
3. The Examiner finds that "[a]ny protein secreted by the trophoectoderm [sic] would . . . be expected to be found within the

[9] The Examiner has stated that claim 31 is not rejected under 35 U.S.C. § 101 and also provides no argument relating to claim 31 with respect to the 35 U.S.C. § 101 rejection. (Ans. 15.) Accordingly, we do not address Appellants' argument regarding claim 31 in the context of this rejection.

blastocoel fluid" and cites Dardik[10] as evidence that trophectoderm proteins are present in blastocoel fluid. (Ans. 30.)

4. Debnath teaches that "[g]landular epithelial cells, such as those in the mammary gland, have several distinguishing histological features including a polarized morphology, specialized cell-cell contacts, and attachment to an underlying basement membrane." (Debnath 256, left column.)

5. Fig. 1A of Debnath is excerpted below:



(Debnath Fig. 1A.) Fig. 1A of Debnath depicts a "[s]chematic (left) of a lobule from human mammary gland" and "[a] hematoxylin- and eosin-stained tissue section (right) of acini within human mammary tissue."[11] (*Id.* at Fig. 1A caption.) Debnath teaches that "mammary epithelium possesses a polarized architecture surrounding a hollow lumen, which is surrounded by an inner layer of luminal epithelial cells and an outer layer of myoepithelial

[10] The Examiner did not provide the full citation to Dardik. However, we understand that the Examiner's citation is to Alan Dardik et al., *Protein secretion by the mouse blastocyst: differences in the polypeptide composition secreted into the blastocoel and medium*, 45 BIOLOGY REPROD. 328 (1991).

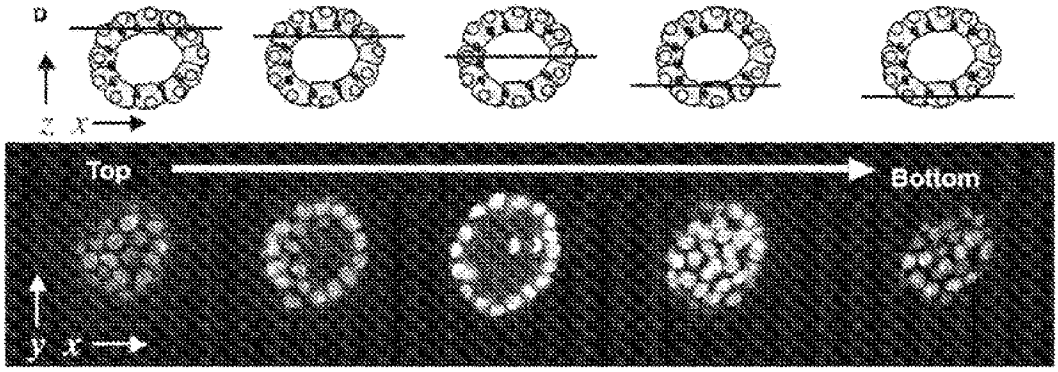
[11] Acini are epithelial cell-lined "pockets" within the mammary gland that can expand when filled with milk.

and basal epithelial cells," and further teaches that "the lumens of mammary acini in vivo often contain proteinaceous secretory material." (*Id.*)

6. Debnath teaches that "mammary epithelial cells grown in three dimensions recapitulate numerous features of breast epithelium in vivo, including the formation of acini-like spheroids with a hollow lumen, apicobasal polarization of cells making up these acini, the basal deposition of basement membrane components (collagen IV and laminin V), and, in some cases, the production of milk proteins." (Debnath 257, left column; *see also id.* at Abstract.)

7. Debnath teaches a specific method of growing mammary epithelial cells from the MCF-10A cell line in three-dimensional culture. (*Id.* at 257, left column (describing MCF-10A cell line); 261–263 (method of growing three-dimensional culture).)

8. Figure 5D of Debnath is excerpted below:



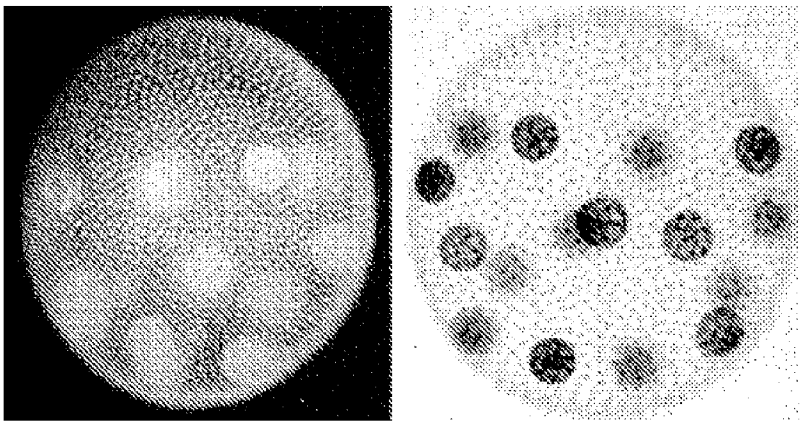
(*Id.* at Fig. 5D.) Figure 5D of Debnath depicts "[s]erial confocal cross sections (x-y axis) through a Day 15 MCF-10A acinus. The schematic diagrams overlying each section illustrate the relative position of the optical section with respect to the z axis." (*Id.* at Fig. 5D caption.)

9. Kirk discloses that volvox "is a spherical multicellular green algae, which contains many small biflagellate somatic cells and a few large, non-motile reproductive cells called gonidia." (Kirk R599, column 1.)

10. Kirk discloses that, during asexual reproduction, "mature gonidium initiates . . . cleavage divisions" to create a "[a] fully cleaved embryo contain[ing] all of the cells of both types that will be present in an adult" but that is inside out, which then undergoes inversion to turn right-side-out. (*Id.* at R599, column 2.)

11. Kirk discloses that, "[f]ollowing inversion, both the adult spheroid and the juvenile spheroids within it increase in size (without further cell division) by depositing large quantities of a glycoprotein-based extracellular matrix. Part way through the expansion phase, the juveniles digest their way out of the parental matrix and become free-swimming." (*Id.*)

12. The sole figure in Kirk is excerpted below:



(Kirk R599.) The figure in Kirk shows "[d]arkfield (left) and brightfield (right) micrographs of a . . . spheroid of *Volvox carteri* containing many small somatic cells and a few large, asexual reproductive cells called gonidia." (*Id.*)

Principles of Law

Patentable Subject Matter

Natural phenomena, including naturally occurring organisms, are not patentable. *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333, 1335–1336 (Fed. Cir. 2014).

In *Funk Brothers*, "bacteria produced by the laboratory methods of culture are placed in a powder or liquid base and packaged for sale to and use by agriculturists in the inoculation of the seeds of leguminous plants." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 129 (1948). The Supreme Court concluded that such a mixture of bacteria was not patent eligible: "The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none." *Id.* at 130; *see also In re Roslin Institute (Edinburgh)*, 750 F.3d at 1336 (explaining that "while the method of selecting the strains of bacteria [in *Funk Brothers*] might have been patent eligible, the natural organism itself—the mixture of bacteria—was unpatentable because its 'qualities are the work of nature' unaltered by the hand of man") (citation omitted).

In *Chakrabarty*, the Supreme Court found that, in contrast to the mixture of bacteria in *Funk Brothers*, "the patentee has produced a new bacterium *with markedly different characteristics from any found in nature* and one having the potential for significant utility." *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980) (emphasis added).

In *Myriad*, the Supreme Court held that "extensive effort alone is insufficient to satisfy the demands of § 101." *Association for Molecular*

Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2118 (2013). The Court further found that Myriad's claims, which relate to isolated DNA of genes that may be examined to determine a person's risk of developing breast cancer, *id.* at 2112–2113, were not "saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule": "Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA." *Id.* at 2118.

Finally, in *Roslin*, the Federal Circuit applied the above Supreme Court case law and found that claims to a "live-born clone" of a donor mammal are not directed to patent-eligible subject matter. *Roslin*, 750 F.3d at 1337. In particular, although patent applicants contended that "copies (clones) are eligible for protection because they are 'the product of human ingenuity' and not 'nature's handiwork, but [their] own,'" the Federal Circuit found that a clone is not patentable because it is "an exact genetic replica" of the donor mammal and "does not possess 'markedly different characteristics from any [farm animals] found in nature.'" *Id.* (brackets in original and citations omitted).

Product-by-Process Claims

"The patentability of a product does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) (citation omitted).

Analysis

Claim 1

In light of Supreme Court and Federal Circuit precedent, we agree with the Examiner that claim 1 is invalid as being directed to non-patentable subject matter.

We begin by noting that claim 1 is a claim to a product, i.e., an artificial gland. Thus, while claim 1 recites that cells are "assembled in three dimensions in a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer," the patentability of the claim does not depend on such methods of production. *In re Thorpe*, 777 F.2d at 697. Given the above, and as also discussed below in Sections IV and VI, we agree with the Examiner that claim 1 reads on natural products, specifically the mouse blastocysts described in Zetter and the volvox algae described in Kirk.[12] (FF1–3, 9–11.)

[12] The Examiner finds that claim 1 also reads on the mammary gland acini described in Debnath, which the Examiner finds to be another example of naturally occurring structure that cannot be distinguished from the structure of claim 1. (Ans. 4.) We are not convinced. Claim 1 requires cells organized to form a membrane, which in turn define an enclosed volume. Although Debnath does disclose acini-like spheroids that reads on claim 1, as discussed further below in Section V, such spheroids are not naturally occurring, but rather grown in three-dimensional culture in vitro. (FF6–FF8.) In contrast, as depicted in Debnath Figure 1A (left), it is not clear that the epithelial cells of the naturally occurring mammary gland acini define an "enclosed" volume, because the epithelial cells do not appear to completely surround the "lumen." (FF5.) Thus, we do not rely on Debnath in affirming the Examiner's rejection of claim 1 under 35 U.S.C. § 101. *Cf. In re Bush*, 296 F.2d 491, 496 (CCPA 1961) (the Board may rely on less than all of the references relied upon by Examiner).

Appellants rely on the 2014 Interim Guidance in arguing that the claims are patentable.[13] We address these arguments below.

Appellants first argue that the claims are patentable because they are directed to a manufacture and composition of matter and because they recite "artificial assembly . . . of cells" that are "assembled in a man-made device." (Appeal Br. 29, 31–32.) As already discussed, the specific process by which the cells are assembled does not confer patentability, because claim 1 is directed to a product. Given that claim 1 is a product claim, we are also not persuaded by Appellants' argument in view of *Myriad* and particularly *Roslin*. In both of those cases, the claimed products—an isolated DNA and a cloned mammal, respectively—are produced only after significant human intervention. The isolated DNA of *Myriad*, for instance, required "sever[ing] chemical bonds and thereby creat[ing] a nonnaturally occurring molecule." *Myriad*, 133 S. Ct. at 2118. Likewise, the cloned mammal in *Roslin* would not have existed without human involvement. Indeed, the method resulting in the clones claimed in *Roslin* "constituted a breakthrough in scientific discovery." *Roslin*, 750 F.3d at 1334. The claims in both of these cases have nevertheless been held to be directed to patent ineligible products of nature, because they do not possess "markedly different characteristics" from products found in nature. *Id.* at 1337 (citation omitted); *Myriad*, 133 S. Ct. at 2117.

Appellants next argue that, even if the claims were considered to be directed to a "natural product," they are patentable because they recite as a

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[13] *2014 Interim Guidance on Patent Subject Matter Eligibility*, 79 Fed. Reg. 74,618 (Dec. 16, 2014), available at https://www.federalregister.gov/articles/2014/12/16/2014-29414/2014-interim-guidance-on-patent-subject-matter-eligibility.

whole something significantly different than the natural product. (Appeal Br. 32–38.) Appellants first contend that the Examiner already admitted that the claimed artificial gland is "***structurally different*** from a naturally occurring gland." (*Id.* at 32–33.) We are not convinced. As the Examiner points out, Zetter and Kirk are not directed to naturally occurring glands as the term gland is conventionally understood. (Ans. 19.) Thus, the Examiner's statement is far from an admission that the blastocysts in Zetter and the volvox algae described in Kirk are structurally different from the claimed artificial gland.

Appellants also argue that the claims "require a structure that is an isolated product existing as an independent unit" as well as a reservoir/bioreactor containing a cell activity product, and that "claim limitations involving 'independent unit' and 'isolated product' are not met by any product found in nature." (Appeal Br. 34–35, 36–37.) We are not persuaded. Both Zetter's blastocysts and the volvox described in Kirk are independent units that may be isolated. (FF2, FF12.) Furthermore, the Supreme Court found in *Myriad* that isolated DNA are not patent eligible, even though such isolated DNA are not found in nature. *Myriad*, 133 S. Ct. at 2118.

Appellants next argue that, "[i]mplicit in this requirement [that cells be assembled into a membrane in a component selected from the group consisting of a flow chamber, a microfluidic device, and an ink jet printer,] is [a requirement] that the cells . . . be structurally fit in order to survive assembly in these machines." (Appeal Br. 35.) We are not persuaded. Appellants provide no persuasive evidence to support the claim that the cells of the claimed artificial gland are more "structurally fit" than those in the

cellular aggregates disclosed in Zetter and Kirk. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974) ("Attorney's argument in a brief cannot take the place of evidence."). Furthermore, Appellants do not suggest that the assembly devices render the cells more structurally fit, and neither the claims nor the Specification suggests any method of treating the cells to render it sufficiently "structurally fit" to survive in machine assembly. Thus, the structural integrity Appellants suggest to be a distinguishing characteristic is nevertheless natural.

Appellants reiterate that the claims require cells be assembled into a membrane in a man-made device and argue that, "[e]ven if the assembly machines are not considered as imbuing any structure to the artificial gland," they impose "meaningful limits on claim scope that avoid substantially foreclosing the use of any natural product." (Appeal Br. 35–36.) As already discussed, this argument is not persuasive in light of *Myriad* and particularly *Roslin*.

Finally, with respect to whether a "[c]laim recites one or more elements/steps in addition to the judicial exception(s) that add a feature that is more than well-understood, purely conventional or routine in the relevant field," Appellants contend that the claims "require a unique combination of materials to create a unique product not before seen or available to enable unique research capabilities and unique treatment possibilities." (Appeal Br. 38.) Such generic attorney argument, without supporting evidence, does not suffice to render the claims patent eligible. *In re Pearson*, 494 F.2d at 1405.

Claims 33 and 34

Claims 33 and 34 require the claimed artificial gland to comprise "*components of a cell* assembled in three dimensions and organized to form

a membrane." (Appeal Br. 97 (Claims App'x) (emphasis added).) Appellants contend that claims 33 and 34 do not recite cells and thus the Examiner's rationale with respect to the 35 U.S.C. § 101 rejection is inapplicable as to these claims. (*Id.* at 30, 34.) The Examiner responds that "an artificial gland produced by a membrane of cells[] is produced by a membrane of cellular components," because "[c]laims 33 and 34 do not require the cell components to be isolated." (Ans. 20.)

We find Appellants have the better argument. The Specification describes the embodiment relating to claims 33 and 34 as one in which "components of a cell are used *instead of* cells." (Spec. ¶ 59.) Thus, we are not persuaded that an artificial gland comprising "components of a cell . . . organized to form a membrane" reads on aggregates of intact cells such as the blastocyst and volvox described respectively in Zetter and Kirk.

Claim 35

Appellants argue that claim 35 is not directed towards a product of nature because no naturally occurring product anticipates or renders obvious the artificial gland recited in claim 35. (Appeal Br. 30.) We are not persuaded because we find that volvox, an algae that occurs in nature, anticipates claim 35, as further discussed below in connection with the rejection of claim 35 under 35 U.S.C. § 102 as anticipated by Kirk.

Claim 36

Appellants argue that claim 36 is not directed towards a product of nature because no naturally occurring product anticipates or renders obvious the artificial gland recited in claim 36. (Appeal Br. 30.) We find Appellants have the better argument. Although the Examiner contends that Zetter, Debnath, and Kirk all disclose "naturally occurring structures that cannot be

distinguished from the structure in claims 1–4, 7, and 33–36," the Examiner has provided no citation to the cited references wherein a specified type of "organized algae micro-colony" is naturally found within a volume enclosed by a membrane formed of cells, as required by claim 36.

Accordingly, we affirm the Examiner's rejection of claims 1 and 35 and reverse the Examiner's rejection of claims 33, 34, and 36 under 35 U.S.C. § 101. Claims 2–4 and 7, which were not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

II.

Issue

The Examiner has rejected claims 1–5, 7, 8, and 13 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. Citing to paragraph 45 of the Specification, the Examiner finds the Specification states "the artificial gland is an independent unit and an isolated product," in contrast to the artificial gland as claimed, which is "made up of an independent unit and something else, where the independent unit consists of an isolated product, the product being undefined." (Ans. 6.)

Appellants appear to agree that the Specification "explains that the artificial gland is the 'isolated product' and is an 'independent unit.'" (Appeal Br. 40.) Appellants argue, however, that "in view of the explanation in the description, a reasonable interpretation of claim 1 would require that the claimed 'artificial gland' is made up as an 'independent unit,' which because of the transitional phrase 'comprising' is an essential, (not an optional) feature" and which further "may not be other than an 'isolated product.'" (*Id.* at 40–41; Reply Br. 32.) Appellants contend that

the Examiner disregarded the "plain meaning of 'independent unit' as a state of being and not as a thing or component in plain view of the express provision in the specification." (Reply Br. 34.) Appellants further argue that "[t]he adequacy of the written description was attested to by a third party declaration." (Appeal Br. 42.)

Appellants do not separately argue the claims, and we limit our analysis to claim 1. The issue with respect to this rejection is whether the evidence of record supports the Examiner's conclusion that the Specification does not describe an artificial gland "comprising" an independent unit.

Findings of Fact

13. The Specification discloses "[a]n artificial gland . . . in the form of an independent unit for promoting biological activity." (Spec. ¶ 11.)

14. The Specification states,

> In its simplest form, the first artificial gland embodiment (100) is essentially first cells (110) surrounding a first reservoir (105) and is an independent micro-scale unit for promoting biological activity.
>
> For all of the embodiments, the artificial gland, as an independent unit, is an isolated product that can be assembled into tissue, organs, or other biological supportive material. Preferably, the artificial gland is in the micron size range of about 10-500 microns. However, larger embodiments up to a centimeter and beyond in diameter are theoretically possible.

(Spec. ¶¶ 44–45.)

Principles of Law

A description adequate to satisfy 35 U.S.C. § 112, first paragraph, must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." In

> other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.

Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (citation omitted, alteration in original).

The Examiner "bears the initial burden . . . of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

> Insofar as the written description requirement is concerned, that burden is discharged by "presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.". . . If the applicant claims embodiments of the invention that are completely outside the scope of the specification, then the examiner . . . need only establish this fact to make out a prima facie case.

In re Alton, 76 F.3d 1168, 1175 (Fed. Cir. 1996) (citation omitted).

Analysis

As set forth above, claim 1 recites an artificial gland "comprising an independent unit for promoting biological activity," the independent unit "consisting of an isolated product," and the artificial gland "further comprising" cells organized to form a membrane defining an enclosed volume and a reservoir within the enclosed volume comprising a bio-reactor containing a product of activity of the cells.

We agree with the Examiner that claim 1 encompasses embodiments outside of the scope of the Specification. In particular, the Specification only describes an artificial gland that is an independent unit and an isolated product. (FF13, FF14.) In using the open transitional phrase "comprising,"

however, claim 1 encompasses artificial glands that *include* an independent unit that is an isolated product, but need not themselves *be* independent units or isolated products.

We note but are not convinced by Appellants' argument that the Examiner's construction of the claim is unreasonable. (Appeal Br. 40–41; Reply Br. 31–34.) While claims are read in light of the Specification, "[c]laim language itself sets the claim scope." *Crystal Semiconductor Corp. v. TriTech Microelectronics Intern., Inc.*, 246 F.3d 1336, 1347 (Fed. Cir. 2001). "When a patent claim uses the word 'comprising' as its transitional phrase," as claim 1 does here, "the use of 'comprising' creates a presumption that the body of the claim is open. In the parlance of patent law, the transition 'comprising' creates a presumption that the recited elements are only a part of the device, that the claim does not exclude additional, unrecited elements." *Id.* at 1348. The Examiner's construction of the claim is consistent with this general tenet of claim construction.

We are likewise unpersuaded by Appellants' argument that "[t]he adequacy of the written description was attested to by a third party declaration" because the Cheng Declaration[14] allegedly "point[ed] to peer[] reviewed scientific reports on the manufacture and use of the artificial gland to be supportive of the operability, functionality and usefulness of the claimed artificial gland." (Appeal Br. 42.) As an initial matter, the "operability, functionality and usefulness" of the claimed invention does not

[14] Declaration of Zhengdong Cheng under 37 C.F.R. § 1.132 (Oct. 25, 2012) ("Cheng Declaration"). The Cheng Declaration is not paginated. Therefore, all reference to page numbers in the Cheng Declaration refer to page numbers as if the Cheng Declaration was numbered consecutively beginning with the first page.

show that the "*disclosure* of the application . . . reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharms.*, 598 F.3d at 1351 (emphasis added). Furthermore, the generic statement in the Cheng Declaration was not supported by analysis of how any of the cited reports is supportive of the operability, functionality and usefulness of the claimed invention. Opinions on ultimate legal issues are not entitled to weight absent supporting evidence. *In re Reuter*, 670 F.2d 1015, 1023 (CCPA 1981) (expert's opinion on ultimate legal issue entitled to no weight).

Accordingly, we affirm the Examiner's rejection of claim 1 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. Claims 2–5, 7, 8, and 13, which were not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

III.

Issue

The Examiner has rejected claims 1–5, 7, 8, 13, and 31–36, because "[t]he specification does not provide guidance for producing or using the claimed artificial gland." (Ans. 8.) The Examiner finds that a gland is "an organ or a tissue that produces and secretes proteins, enzymes or hormones . . . either constitutively or regulated by a signal from outside the gland." (*Id.*) The Examiner finds that the claims are not enabled because the claimed structure "lacks the mechanism for either constitutive release or regulated release" and because the Specification fails to provide guidance for obtaining such release. (*Id.* at 9–10.) The Examiner finds that there is no enablement commensurate with the full scope of the claims, because the

claimed reservoir can be water, gas, or gel, but the Specification "provides no guidance as to the type of gas that would solubilize proteins, enzymes or hormones." (*Id.*) The Examiner further finds that the claims are not enabled because the Specification fails to provide guidance as to how to overcome any immune response to the claimed structure or how to obtain organ regeneration either in vivo or in vitro through use of the claimed structure. (*Id.* at 10.) Finally, the Examiner finds that claims 33 and 34 further lacks enablement because the Specification "does not provide guidance for the formation of an artificial gland that contains a membrane of cellular components," [15] as required by these claims, or how such a gland may be used "for drug testing, tumor biology and organ/tissue regeneration or replacement" as disclosed in the Specification. (*Id.* at 11–12.)

With respect to claims 33 and 34,[16] Appellants argue that the Examiner erroneously assumes without basis that self-aggregation to form a membrane is cell-dependent. (Appeal Br. 44–45.) Appellants did not address the enablement rejection of the remaining claims in the Appeal Brief, but argue in the Reply Brief that the enablement requirement is satisfied with respect to the term "artificial gland" because of "the potential of a group of cells making up the shell to deliver the contents of the

[15] Both the Examiner and Appellants direct their arguments relating to formation of an artificial gland using components of a cell to claims 31 and 32. (Ans. 11–12; Appeal Br. 44–45.) As the Examiner points out in response to Appellants' arguments, however, such arguments appear properly directed towards claims 33 and 34. (Ans. 26.) Appellants did not dispute this characterization of the arguments in the Reply Brief; accordingly, we analyze these arguments as though they are directed towards claims 33 and 34.

[16] *See supra* note 13.

reservoir" and in view of an expert declaration[17] that purportedly "point[s] to peer[] reviewed scientific reports on the manufacture and use of the artificial gland [that are] supportive of the operability, functionality and usefulness of the claimed artificial gland." (Reply Br. 34–36 (citing Appeal Br. 41–43).) Appellants also argue that the Examiner's construction of the term "gland" is unduly narrow. (*Id.* at 35–36.) With respect to the Examiner's argument that the enablement is not commensurate with the scope of the claims because the Specification does not enable a "reservoir" that is a gas, Appellants argue that the Specification teaches a method of making the artificial gland wherein a gas is introduced into a microchannel, and further argue that there is no requirement that the claimed reservoir "solubilizes proteins" as suggested by the Examiner. (*Id.* at 36–37.) Finally, Appellants argue that the Examiner has cited no evidence that undue experimentation would be needed to implement the invention as claimed. (*Id.* at 37.)

The issue with respect to this rejection is whether the evidence of records supports the Examiner's conclusion that the Specification does not enable a skilled artisan to make and use the claimed artificial gland.

Findings of Fact

15. The Specification states that an artificial gland is

> a "living capsule" with a biomembrane (tissue) shell and a unique core that acts as container or reservoir. . . . The reservoir is a bio-reactor capable of containing a product of activity of the cells. The reservoir preferably comprises a gas, a liquid, or a gel and preferably also contains nanoparticles, a buffer, a surfactant, and, a gel precursor. The reservoir may

[17] Appellants do not reference a specific expert declaration; however, we assume Appellants to be referring to the previously discussed Cheng Declaration.

> also contain cells. Nanoparticles may also surround the artificial gland to form a protective coating.

(Spec. ¶ 11; *see also id.* at ¶¶ 18–19, 26.)

16. The Specification states that "[t]he contents of the bio-reactor preferably include a substance comprising a fluid in the form of a gas, liquid, gel, or a combination of these." (*Id.* at ¶ 48.)

17. The Specification states that "the artificial gland is useful for biological tissue and organ repair and replacement and stem cell engineering and biotechnology applications." (*Id.* at ¶ 2; *see also id.* at ¶¶ 3, 7, 13–16, 21, 27–28, 53, 168, 169, 173–175, 214, 220.) In particular, the Specification states that the artificial gland "is capable of being used to support the growth of organs and other biological material without the use of macro-scale scaffolds" and "can control the 3-dimensional arrangements of cells and subcellular systems in such a way that can mimic nature." (*Id.* at ¶ 18; *see also id.* at ¶¶ 20–24, 28 (application to 3-D in vitro cell cultures), 52 ("[s]hape variability [of artificial gland] . . . broadens the parameter-space for the design of any type of artificial tissue, and can help to direct strategies for all types of tissue engineering"), 56, 149.) The Specification further indicates that claimed artificial glands have applications in the treatment of diseases. (*Id.* at ¶¶ 56, 171, 178–180, 189, 194, 207, 209–210.)

18. The Specification states that "[the] artificial glands with a membrane of cells and a central reservoir . . . create opportunities to trigger events that can lead to . . . vehicles for food and pharmaceutical applications." (*Id.* at ¶ 13; *see also id.* at ¶¶ 21, 23, 25 ("new means for manipulating controlled releases or absorptions supporting biological activity," "tuning rheological or optical properties of cosmetics, foods, or

other fluids," and "functionaliz[ation] for a specific biological tasking"), 149–152.)

19. The Specification indicates that the claimed artificial glands have applications in drug or therapy screening and in modeling disease states for study. (*Id.* at ¶¶ 56, 170, 172, 176, 211–213.)

20. The Specification states,

> An alternative embodiment of the artificial gland uses the same configuration and components as described above, except that biological units are used instead of cells. The biological units form a membrane. . . . Biological units are similar in that they perform a biological activity that produces products, but they may not be classified as living. Biological units include fungi, algae, spores, pollen, yeast, bacteria, and viruses.
>
> An alternative embodiment of the artificial gland uses the same configuration and components as described above, except that components of a cell are used instead of cells. The components of a cell form a membrane assembled in three dimensions. . . . Components of a cell are similar in that they perform a biological activity that produces products, but they are not classified as living. Examples of components of a cell are: enzymes, prions, hormones, growth factors, Tumor Necrosis Factor-alpha, Tumor Necrosis Factor-beta, cytokines, interleukins, albumin-scavengers, polyclonal-anti-bodies, monoclonal-anti-bodies, immunoglobulines, protease enzymes, lysosomes, vesicles, cell membranes, rough endoplasmic reticulums, smooth endoplasmic reticulums, mitochondria, ribosomic ribonucleic acid, transference ribonucleic acid, deoxyribonucleic acid, mitrotubules, endocrine cells, and human T-cells, fatty acids, beta-OH-butirate, acetoacetate, polycations, poly L lisine, ornithine, chitosan, oligoelements, genes, chloroplasts, chlorophyll, glucidic elements.

(*Id.* at ¶¶ 58–59.)

Principles of Law

> Section 112 requires that the patent specification enable those skilled in the art to make and use the full scope of the claimed invention without undue experimentation . . . . [*S*]*ee also In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993) ("[T]he specification must teach those of skill in the art how to make and how to use the invention as broadly as it is claimed.") . . . .

Invitrogen Corp. v. Clontech Labs. Inc., 429 F.3d 1052, 1070–71 (Fed. Cir. 2005) (citation and internal quotation marks omitted).

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

"[T]he enablement requirement of § 112 incorporates the utility requirement of § 101." *In re Fisher*, 421 F.3d 1365, 1378 (Fed. Cir. 2005). Courts "have required a claimed invention to have a specific and substantial utility to satisfy § 101." *Id.* at 1371.

> [A]n application must show that an invention is useful to the public as disclosed in its current form, not that it may prove useful at some future date after further research. Simply put, to satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public.

Id.

To satisfy "the 'specific' utility requirement, an application must disclose a use which is not so vague as to be meaningless. . . . Thus, in

addition to providing a 'substantial' utility, an asserted use must show that th[e] claimed invention can be used to provide a well-defined and particular benefit to the public." *Id.* "Nebulous" expressions such as "biological activity" or "biological properties," and "obscure" expressions such as "useful for technical and pharmaceutical purposes" do not suffice to provide specific utility. *Id.*

"Enablement, or utility, is determined as of the application filing date." *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995). "It is an applicant's obligation to supply enabling disclosure without reliance on what others may publish after he has filed an application on what is supposed to be a completed invention. If he cannot supply enabling information, he is not yet in a position to file." *In re Glass*, 492 F.2d 1228, 1232 (CCPA 1974).

Analysis

Appellants address only claims 33 and 34 in its Appeal Brief with respect to the enablement rejection; accordingly, we limit our analysis of this rejection to these two claims and summarily affirm the Examiner's enablement rejection of claims 1–5, 7, 8, 13, 31, 32, 35, and 36.[18]

[18] Appellants make additional arguments that are applicable to the other rejected claims in their Reply Brief. These arguments are waived, however, because they were not presented in the opening brief, thereby denying the Board the benefit of the Examiner's response, and no showing of good cause was made by Appellants to explain why the late argument should be considered by the Board. *See* 37 C.F.R. § 41.41(b)(2); *Cf. Optivus Technology, Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 989 (Fed. Cir. 2006) (argument raised for the first time in the Reply Brief that could have been raised in the opening brief is waived).

Claim 33 requires the claimed artificial gland to comprise "components of a cell assembled in three dimensions and organized to form a membrane." (Appeal Br. 97 (Claims App'x).) Claim 34, which depends from claim 33, clarifies that the components of the cell encompassed within claims 33 and 34 include, among others:

> enzymes, prions, hormones, growth factors, Tumor Necrosis Factor-alpha, Tumor Necrosis Factor-beta, cytokines, interleukins, albumin-scavengers, polyclonal-anti-bodies, monoclonal-anti-bodies, immunoglobulines [sic], protease enzymes, lysosomes, vesicles, cell membranes, rough endoplasmic reticulums, smooth endoplasmic reticulums, mitochondria, ribosomic ribonucleic acid, transference ribonucleic acid, deoxyribonucleic acid, mitrotubules [sic microtubules ?], endocrine cells, and human T-cells, fatty acids, beta-OH-butirate [sic butyrate], aceto acetate, polycations, poly L lisine [sic lysine], ornithine, chitosan, oligoelements, genes, chloroplasts, chlorophyll, [and] glucidic elements.

(*Id*. at 97–98.)

We agree with the Examiner that claims 33 and 34 fail to satisfy the enablement requirement because the Specification "does not provide guidance for the formation of an artificial gland that contains a membrane of cellular components" or how such a gland may be used "for drug testing, tumor biology and organ/tissue regeneration or replacement" as disclosed in the Specification. (Ans. 11–12.) We note that there are no working examples of an artificial gland comprising a membrane of cellular components,[19] and only minimal, if any, other direction or guidance in the

[19] While the Specification discloses "a method of artificial gland production implemented as a proof of concept," the method uses cells (specifically yeast cells) rather than cell components. (Spec. ¶ 77; *see also id*. at ¶ 215 (stating that "[a]n artificial gland constructed with a fibroblast membrane has been constructed for testing the invention"), ¶ 169 (stating that "[a]rtificial micro-

Specification regarding how to make a membrane composed from other cellular components. *In re Wands*, 858 F.2d at 737 (describing factors to be considered in determining enablement). Furthermore, none of the prior art cited by the Examiner describes such a membrane of cellular components, and the scope of the claims 33 and 34 is extremely broad, encompassing components as divergent as genes and chlorophyll. *Id.*

Appellants argue that the Specification "explains that the mechanism forming the artificial gland using *components of a cell* operates in the same way as for cells," "indicates that the mechanism employed is non-cellular dependent," and "explains that self-aggregation may be aided by the ability to control non-cellular-related physical factors associated with the assembly environment." (Appeal Br. 44–45.) We are not persuaded. While we understand Appellants assert that the same basic factors of, e.g., minimization of interfacial energy and electrostatic interaction, affect the formation of a membrane composed of cellular components as well as that composed of cells, the Specification provides no support that such factors would affect cells and all the claimed cellular components ***in the same way so as to lead to creation of a membrane***. Neither does the Specification provide any guidance on how such factors should be adjusted in view of the differences between cells and the many different types of cellular components claimed.

Appellants further argue that "[t]he embodiments involving components of cells may be used in many of the same research activities as

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glands were suspended separately in a concentrated phosphate buffered saline solution [and] subsequently printed as a kind of 'ink' onto several []biopapers made from soy agar and collagen gel").)

other embodiments." (*Id.* at 45–46.) We are likewise not persuaded. Appellants' broad statements regarding potential use of the claimed artificial glands (FF17–19) do not describe the "specific and substantial" utility needed to satisfy the enablement requirement. Generic statements that the claimed artificial gland is useful for "biological tissue and organ repair and replacement," "stem cell engineering," "biotechnology applications," "treatment of diseases," "vehicles for food and pharmaceutical applications," or "applications in drug or therapy screening and in modeling disease states for study" are too vague to provide ***specific*** utility. *In re Fisher*, 421 F.3d at 1371.

Similarly, these statements do not provide substantial utility because they suggest that the claimed artificial gland "may prove useful at some future date after further research," but do not show that it is "useful to the public as disclosed in its current form." *Id.* The Specification states, for example, that the claimed artificial gland "holds ***the potential*** to play a vital role in tissue engineering, stem cell engineering, synthetic biology, and in the design of multicellular vehicles for food and pharmaceutical applications." (Spec. ¶ 21 (emphasis added).)

Finally, while working examples are not ***necessary*** to satisfy enablement, they are desirable in complex technologies, and we note that the Specification provides no such examples of using the claimed artificial gland. *In re Strahilevitz*, 668 F.2d 1229, 1232 (CCPA 1982) (working examples desirable but not necessary); *In re Fisher*, 421 F.3d at 1377 (finding lack of specific and substantial utility because "[applicant's] laundry list of uses, like the terms 'biological activity' or 'biological properties' alleged in *Kirk*, are nebulous, especially in the absence of any

data demonstrating the claimed [inventions] were actually put to the alleged uses").

Accordingly, we affirm the Examiner's rejection of claims 1–5, 7, 8, 13, and 31–36 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the enablement requirement.

IV.

Issue

The Examiner rejects claims 1, 2, 4, 7, 33, and 34 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Zetter. As discussed above, the Examiner finds that Zetter teaches a mouse blastocyst containing an outer layer of trophectoderm cells enclosing a fluid-filled cavity (the blastocoel), with the pluripotent ICM at one end of the blastocoel. (Ans. 13.) The Examiner finds that "[n]o distinction between the mouse blastocyst taught by Zetter and the claimed invention [exists,]" because Zetter's blastocyst "comprises cells forming a membrane around a fluid filled cavity, the blastocoel, containing proteins secreted by the cells, [together with] additional cells, the ICM." (*Id.* at 13–14.)

Appellants contend that Zetter does not teach that the fluid-filled cavity of the blastocyst contains any product of the trophectoderm. (Appeal Br. 47.) Appellants also contend that the blastocyst disclosed in Zetter is not "an independent unit" or "an isolated product." (*Id.* at 49–50.) Appellants further contend that Zetter does not teach an artificial gland with the structural limitations implicit in the claimed method of assembly. (*Id.* at 51–52.) Citing *Chakrabarty*, the Specification, various news articles, and the

Cheng Declaration, Appellants further argue that the invention "involves a manufactured or artificial gland with 'markedly different characteristics'" than natural products, including "robust tissue structural characteristics that enable many uses not found in nature." (*Id.* at 53–56.) Finally, Appellants contend that Zetter does not disclose a membrane made of "components of a cell" as required by claims 33 and 34.[20] (*Id.* at 48.)

Appellants do not separately argue claims 2, 4, and 7, and we therefore limit our analysis to claims 1, 33, and 34. The issue with respect to this rejection is whether the evidence of record supports the Examiner's conclusion that claims 1, 33, and 34 are anticipated or rendered obvious by Zetter.

Analysis

Claim 1

As an initial matter, claim 1 is directed to a product (i.e., an artificial gland), even though it also recites limitations regarding the process used to create such a product. As noted earlier, "[t]he patentability of a product does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d at 697. Zetter discloses all of the structural limitations of claim 1; accordingly, the evidence of record supports the Examiner's finding that Zetter anticipates claim 1.

[20] Appellants also argue that Zetter does not disclose the volvox algae and algae micro-colony required by claims 35 and 36. (Appeal Br. 49.) The Examiner has removed claims 35 and 36 from the anticipation rejection over Zetter. (Ans. 30.) Accordingly, we do not address Appellants' arguments regarding claims 35 and 36 with respect to this rejection.

Zetter teaches a mouse blastocyst containing an outer layer of trophectoderm cells enclosing a fluid-filled cavity (the blastocoel), with the pluripotent ICM at one end of the blastocoel. (FF1.) Thus, Zetter teaches cells assembled in three dimensions and organized to form a membrane (i.e., the trophectoderm), with the membrane configured to define an enclosed volume (i.e., the blastocoel). Furthermore, the blastocyte is an independent unit and an isolated product within the broadest reasonable interpretation of those terms, as Zetter describes isolating them from the oviduct or uterus of the mouse. (FF2.) Given the substantial identity between the structure described in Zetter and the claimed structure, we also find that the Examiner has established a prima facie case that the blastocoel contains a product of the activity of the cells in the trophectoderm. *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990) (explaining that "when the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not"). Neither have Appellants disputed in the Reply Brief the Examiner's citation to Dardik as evidence that the blastocoel in Zetter's blastocyst contains trophectoderm proteins. (Ans. 30.)

Zetter studies the expression of LETS protein in mouse embryos. (Zetter Abstract.) Appellants contend that Zetter teaches that the LETS protein is ***not*** produced by the trophectoderm and that Zetter thus does not disclose "a reservoir . . . containing a product of activity of the cells." (Appeal Br. 47–48.) We are not persuaded because the Examiner finds that the blastocoel contains other, non-LETS proteins that are produced by the trophectoderm (Ans. 30), and, as discussed, Appellants have not disputed this finding in the Reply Brief.

Appellants also contend that Zetter does not teach an artificial gland with the structural limitations achieved by the claimed method of assembly. (*See generally* Appeal Br. 50–56.) Appellants first argue that the Examiner is inconsistent in simultaneously finding that "***the artificial gland claimed cannot be distinguished from a naturally occurring gland***" and that "[t]he present claims are not enabled because it is ***structurally dissimilar from a naturally occurring gland*** in that the structure lacks the mechanism for either constitutive release or regulated release." (*Id.* at 50.) We are not persuaded. As the Examiner points out, regardless of whether Zetter's blastocyst or the claimed structure is referred to as a "gland" and whether each may be considered structurally similar to a "naturally occurring gland," the significant point for purposes of the anticipation rejection is that Zetter discloses all of the ***structural*** limitations recited ***in the claims***. (Ans. 32.)

Neither are we convinced by Appellants' reliance on *Chakrabarty*, the Specification, various news articles, the Cheng Declaration, and attorney argument in contending that the invention "involves a manufactured or artificial gland with 'markedly different characteristics'" than natural products, including "robust tissue structural characteristics that enable many uses not found in nature." (Appeal Br. 53–56.) As further discussed below, while we agree that claim 1 may be patentable over Zetter if the method of production recited in the claim in fact results in structural differences, Appellants have not provided persuasive evidence that such structural differences exist.[21]

[21] For this reason, Appellants' citation to *Chakrabarty* is unavailing. The artificial, genetically engineered microorganism in *Chakrabarty* was genetically distinct (i.e., structurally different) from the naturally occurring microorganism. *Chakrabarty*, 447 U.S. at 305, 309–310.

With respect to Appellants' argument that "the limitation specifying how the cells are assembled . . . is an implicit structural limitation because qualifying cells must be structurally viable to withstand the relatively fast acting assembly mechanism," we note that "[a]ttorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d at 1405. For the same reason, we are not persuaded by Appellants' citation to the Specification regarding the ability of the claimed gland to "eliminate[] the need for a macro-scale tissue-shaping scaffold" and argument in the brief that "[n]o natural product has tissue structural characteristics that eliminate the need for a scaffold and such characteristics are only manifest if the manufactured object is both an independent unit and an isolated product." (Appeal Br. 54.)

Neither do the cited news articles and the Cheng Declaration provide evidence of any structural difference between the claimed artificial gland and Zetter's blastocyst. The news articles provide generic descriptions of "celloidosomes," which Appellants contend are the subject of the claims. Likewise, while the Cheng Declaration states that "[f]ungi, [a]lgae, [b]acteria and also a diverse group of mammalian cells . . . can be 'self-assembled' on gas-liquid interfaces of microbubbles, to form stable micro-core/shell tissues as described . . . in [the] patent application" (Cheng Decl. 2), and that "the artificial gland produced with algal and bacterial cells do form membranous (tissue and/or biofilm) structure and . . . secrete products of the cells from and into the core (reservoir) when used in vitro" (*id.* at 4),

such statements do not support Appellants' contention that the resulting artificial gland differs ***structurally*** from Zetter's blastocyst.[22]

Finally, we note, but are not persuaded by, Appellants' argument that the blastocyst disclosed in Zetter is not "an independent unit" or "an isolated product." (Appeal Br. 49–50.) As already discussed above, the blastocyst described in Zetter is isolated from the oviduct or uterus of the mouse. (FF2.)

Claims 33 and 34

With respect to claims 33 and 34, we find Appellants to have the better argument. As discussed earlier, these claims require "*components* of a cell" assembled in three dimensions and organized to form a membrane. (Appeal Br. 97 (Claims App'x; emphasis added).) The Examiner argues that claims 33 and 34 read on intact trophectoderm cells surrounding blastocoel fluid because "there is no requirement the components be isolated" and trophectoderm cells are made of cell components. (Ans. 30.) As also discussed above, however, the Specification describes the embodiment as one in which "components of a cell are used *instead of* cells." (Spec. ¶ 59 (emphasis added).) Thus, we are not persuaded that the limitation "components of a cell . . . organized to form a membrane" reads on a membrane formed from intact cells.

Accordingly, we affirm the Examiner's rejection of claim 1 as anticipated by Zetter but reverse the rejection of claims 33 and 34 on this

[22] As already discussed, opinions in the Cheng Declaration on ultimate legal issues, such as the statement that "the claimed artificial gland [is] a unique innovation," are not entitled to weight absent supporting evidence. *In re Reuter*, 670 F.2d at 1023.

ground. Claims 2, 4, and 7, which were not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

V.

Issue

The Examiner rejects claims 1, 2, 4, 7, 33 and 34 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Debnath. The Examiner finds that

> Debnath teaches the in vitro formation of mammary gland acini possessing a hollow luminal space surrounded by cells, containing milk protein secretion products from the cells. The acini are about 50 microns in diameter. The mammary gland acini is comprised of mammary epithelial cells surrounding a hollow, which would be air filled, . . . containing secreted milk proteins and tissue fluid. No distinction [exists] between the mammary gland acini taught by Debnath and the claimed invention. Thus, Debnath anticipates or makes obvious the claimed invention.

(Ans. 14 (citations omitted).)

Relying on essentially the same citations and arguments they relied on with respect to the rejection over Zetter, Appellants contend that Debnath does not teach an "artificial" gland and does not teach the structural limitations implicit in the claimed method of assembly. (Appeal Br. 66–71.) Appellants further argue that Debnath does not teach "a cellular membrane surrounding a reservoir that contains a product of activity of the cells of the membrane." (Appeal Br. 64–65.) Finally, Appellants contend that claim 33 does not recite membrane formed from cells and that the Examiner's

rationale as to anticipation by or obviousness over Debnath is thus inapplicable as to this claim.[23] (*Id.* at 63; Reply Br. 38–39.)

Appellants do not separately argue claims 2, 4, and 7, and we limit our analysis to claims 1, 33, and 34. The issue with respect to this rejection is whether the evidence of record supports the Examiner's conclusion that claims 1, 33, and 34 are anticipated or rendered obvious by Debnath.

Analysis

Claim 1

The evidence of record supports the Examiner's finding that Debnath anticipates claim 1. Debnath discloses a method of growing mammary epithelial cells from the MCF-10A cell line in three-dimensional culture. (FF7.) Debnath teaches that mammary epithelial cells grown in three dimensions form "acini-like spheroids with a hollow lumen." (FF6, FF8.) Accordingly, Debnath teaches cells assembled in three dimensions and organized to form a membrane (i.e., the outer cellular layer of the acini-like spheroid), with the membrane configured to define an enclosed volume (i.e., the hollow lumen). Furthermore, the acini-like spheroid is an independent unit and an isolated product within the broadest reasonable interpretation of those terms. (FF8 (depicting confocal cross sections of an individual acini-like spheroid).) Given the substantial identity between the structure described in Debnath and the claimed structure, we also find that the Examiner has established a prima facie case that the lumen of the acini-like

[23] Claim 34 depends from claim 33; thus, we address claims 33 and 34 together. Appellants makes similar arguments with respect to claim 31. (Appeal Br. 63.) However, the Examiner does not appear to have rejected claim 31 over Debnath, and we do not address arguments relating to claim 31 here.

spheroid contains a product of the activity of the cells. *In re Spada*, 911 F.2d at 708. In addition, Debnath teaches that "the lumens of mammary acini in vivo often contain proteinaceous secretory material" and further teaches that, at least in some cases, mammary epithelial cells grown in three dimensions produces milk proteins. (FF5, FF6.)

As they do with Zetter and relying on essentially the same citations to *Chakrabarty*, the Specification, various news articles, and the Cheng Declaration, Appellants contend that Debnath does not teach an artificial gland having the structural limitations implicit in the claimed method of assembly. (Appeal Br. 66–67.) These arguments are not persuasive for similar reasons as those discussed above with respect to the rejection over Zetter. Furthermore, Appellants do not explain why Debnath's cells grown in culture would not be considered "artificial" rather than a "natural product." (*Id.* at 66.)

As further discussed below, we are also not persuaded by Appellants' arguments that "[t]he human mammary tissue shown in Debnath Fig. 1A is not an encircling cellular membrane," that Debnath's acini lumens are not reservoirs within the meaning of the claim, and that Debnath does not teach "a cellular membrane surrounding a reservoir that contains a product of activity of the cells of the membrane." (*Id.* at 64–65.)

While Appellants argue that Debnath's Figure 1A does not show an encircling membrane, Figure 5, which provides "[r]epresentative confocal microscopic imaging of MCF-10A acini," shows that the mammary epithelial cells do in fact form a sphere that completely enclose the lumen when they are grown in three-dimensional culture. (FF8.) For the same reason, Appellants' citation to Merriam-Webster for the definition of lumen,

and the corresponding argument that a lumen is "a tubular cavity" and thus not a "reservoir enclosed by a cellular membrane" is unavailing. Appellants have not pointed out a structural difference between the lumen disclosed in, e.g., Fig. 5 of Debnath, and the reservoir recited in claim 1 and described in the Specification. (*See also* Spec. ¶ 47 ("The shape of th[e] configuration [of membrane formed from a plurality of cells] may be spherical, spheroidal, discoid, cylindrical, tubular or any other three-dimensional shape that physically defines an internal micro-scale volume.").)

Finally, to the extent Appellants are making a separate argument that Debnath does not disclose secretion products in the acini lumen that are "products of activity of the cells" forming the membrane, we disagree for the reasons already discussed: Debnath disclose a structure substantially similar to the claimed structure, and further teaches that "the lumens of mammary acini in vivo often contain proteinaceous secretory material" and that, at least in some cases, mammary epithelial cells grown in three dimensions produces milk proteins. (FF5, FF6.) In sum, the Examiner has demonstrated "sound basis for believing that the products of the applicant and the prior art are the same," and Appellants have not met the burden of showing that they are not. *In re Spada*, 91 F.2d at 708.

Claims 33 and 34

We find Appellants to have the better argument for claims 33 and 34, for the same reason as discussed above with respect to Zetter.

Accordingly, we affirm the Examiner's rejection of claim 1 as anticipated by Debnath but reverse the rejection of claims 33 and 34 on this ground. Claims 2, 4, and 7, which were not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

VI.

Issue

The Examiner rejects claims 1, 2, 4, 7, and 33–36 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Kirk, as evidenced by Volvox Study Guide. The Examiner finds that

> Kirk teaches volvox is a spherical multicellular green alga containing many small biflagellate somatic cells and non-motile gonidia, and moves by a rolling motion. The volvox spheroid contains within its core extracellular matrix and juvenile spheroids. [As evidenced by the Volvox Study Guide,] [t]he volvox spheroid is 350-500 microns in size. Thus, the volvox spheroid is composed of volvox cells that form a membrane surrounding a gel center that contains cells as well as secreted volvox proteins, the extracellular matrix. Volvox meets the limitations of the claims. No distinction [exists] between the Volvox taught by Kirk and the claimed invention. Thus, Kirk anticipates or makes obvious the claimed invention.

(Ans. 14–15 (citations omitted).)

Appellants contend that Kirk does not teach "a 'membrane' of volvox cells formed to create a reservoir as specified for claim[] 32."[24] (Appeal Br. 58.) With respect to claims 33 and 34, Appellants argue that Kirk does not disclose a membrane made of components of a cell. (*Id.* at 59.) With respect to claims 35 and 36, Appellants further argue that Kirk does not disclose a volvox algae or algae micro-colony within any reservoir formed by a membrane. (*Id.*) In the Reply Brief, Appellants further argue that Kirk does not disclose "a membrane formed of cells in machinery in a particular

[24] The Examiner does not appear to have rejected claim 32 over Kirk. We thus understand Appellants to be referring to claim 1 in this statement.

manner and that once formed are an isolated, independent unit," as required by claim 1. (Reply Br. 41.)

Appellants do not separately argue claims 2, 4, and 7. We therefore limit our analysis to claims 1 and 33–36. The issue with respect to this rejection is whether the evidence of record supports the Examiner's conclusion that claims 1 and 33–36 are anticipated or rendered obvious by Kirk.

Analysis

Claim 1

We find that the Examiner has established a prima facie case of anticipation of claim 1 in view of Kirk. Kirk teaches that volvox is a spherical multicellular algae that contains many small somatic cells and a few large non-motile reproductive cells. (FF9.) Kirk teaches that following asexual reproduction adult volvox comprises an outer layer of cells surrounding an enclosed volume containing juvenile volvox spheroids and glycoprotein-based extracellular matrix deposited by the volvox. (FF10–12.) Accordingly, Kirk teaches the volvox as comprising cells assembled in three dimensions and organized to form a membrane, with the membrane configured to define an enclosed volume. Furthermore, the volvox is an independent unit and an isolated product within the broadest reasonable interpretation of those terms. (FF12 (figure depicting a spheroid of *Volvox carteri*); *see also* FF9–FF11.) Finally, Kirk discloses that the enclosed volume contains a product of the activity of the membrane of cells, namely the glycoprotein-based extracellular matrix. (FF11.)

Appellants contend that Kirk teaches composition of volvox cells, not "a 'membrane' of volvox cells formed to create a reservoir as specified for

claim[] 32."[25] (Appeal Br. 58.) In particular, Appellants contend that "applicants' ***membrane*** (outer shell) must be made of more than one cell, not simply confine other cells within the outer shell," and "Kirk has no teaching that the outer structure of the volvox cell is multi-cellular." (*Id.*) Applicants' apparent argument is that Kirk discloses the volvox as a single cell containing many somatic cells and a few larger reproductive cells. (*Id.*) We are unpersuaded by this strained reading of Kirk's disclosure, which also contradicts Appellants' own description of the volvox in the Specification:

> Volvox algae, or simply volvox, is one of the best-known chlorophytes and is the most developed in a series of genera that form spherical colonies. ***Each mature volvox colony is composed of numerous flagellate cells . . . , up to 50,000 in total, and embedded in the surface of a hollow sphere*** or coenobium containing an extracellular matrix made of a gelatinous glycoprotein.

(Spec. ¶ 143.)

In the Reply Brief, Appellants argue for the first time that Kirk does not disclose "a membrane formed of cells in machinery in a particular manner and that once formed are an isolated, independent unit," as required by claim 1. (Reply Br. 41.) Appellants have waived this argument since it was not presented for the first time in the opening Appeal Brief. *Ex parte Borden*, 93 USPQ2d 1473, 1473–74 (BPAI 2010) ("informative"[26]) (absent a showing of good cause, the Board is not required to address an argument newly presented in the reply brief that could have been presented in the principal brief on appeal). In any event, as already discussed, a

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[25] The Examiner does not appear to have rejected claim 32 over Kirk. We thus understand Appellants to be referring to claim 1 in this statement.
[26] Designated as an "Informative Opinion" at http://www.uspto.gov/ip/boards/bpai/decisions/inform/index.jsp.

volvox is an isolated, independent unit, and furthermore "[t]he patentability of a product does not depend on its method of production." *In re Thorpe*, 777 F.2d at 697.

Claims 33 and 34

We find Appellants to have the better argument for claims 33 and 34, for the same reason as discussed above with respect to Zetter.

Claim 35

With respect to claim 35, Appellants argue that Kirk does not disclose a volvox algae within any reservoir formed by a membrane. (Appeal Br. 59.) We are not convinced. Claim 35 recites an artificial gland comprising "cells assembled in three dimensions and organized to form a membrane . . . defining an enclosed micro-scale volume," where "[the] reservoir within the enclosed micro-scale volume . . . comprise[s] volvox algae." (*Id.* at 98 (Claims App'x).) Kirk discloses that, following asexual reproduction, the juvenile volvox spheroids are contained within the adult spheroid until they "digest their way out of the parental matrix and become free-swimming." (FF11.) Thus, Kirk discloses volvox algae (i.e., the junior volvox spheroids) within a reservoir formed by a membrane of the adult volvox, which is in turn formed of multiple cells as discussed above.

Claim 36

With respect to claim 36, Appellants further argue that Kirk does not disclose a claimed algae micro-colony within any reservoir formed by a membrane. (Appeal Br. 59.) We find Appellants have the better argument. Claim 36 requires an artificial gland comprising "cells assembled in three dimensions and organized to form a membrane . . . defining an enclosed micro-scale volume," where "[the] reservoir within the enclosed micro-scale

volume . . . comprise[s] an organized algae micro-colony selected from the group consisting of diatoms, cyanobacteria, pediastrum, hydrodictyon, chlorella, paramecium bursania, Haematococcus pluvialis, spirogyra, mougeotia and zygnema." (*Id.* at 98–99 (Claims App'x).) The Examiner has not explained how Kirk discloses or renders obvious a reservoir comprising an algae micro-colony selected from the recited species.

Accordingly, we affirm the Examiner's rejection of claims 1 and 35 as anticipated by Kirk, but reverse the rejection of claims 33, 34, and 36 on this ground. Claims 2, 4, and 7, which were not separately argued, fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

VI.

Issue

The Examiner rejects claims 1, 2, 4, 5, and 33–36 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Napolitano. The Examiner finds that "Napolitano teaches a hydrogel core surround[ed] by fibroblast cells or fibroblast and endothelial cells . . . . Hydrogel is a nanoparticle[;] thus, the reservoir comprises nanoparticles. Thus, Napolitano clearly anticipates the claimed invention." (Ans. 15 (citations omitted).)

Appellants contend that Napolitano teaches "[a] spheroid of cells formed in the bottom of recesses of a gel," which Appellants argue is "a completely different structure than cells 'organized to form a membrane . . . to define an enclosed volume,' as specified in applicants' claim 1." (Appeal Br. 61.) Appellants also argue that Napolitano does not disclose the spheroid containing "a product of activity of the cells forming that spheroid." (*Id.*) Appellants argue that the Examiner's finding of

anticipation with respect to Napolitano fails to cite all of the limitations of claims 1, 2, 4, and 5. (*Id.*) With respect to claims 33 and 34, Appellants argue that Napolitano does not disclose "a membrane assembled from 'components of a cell.'" (*Id.* at 62.) With respect to claims 35 and 36, Appellants argue that Napolitano does not disclose a volvox algae or an algae micro-colony within the alleged reservoir. (*Id.*)

The issue with respect to this rejection is whether the evidence of record supports the Examiner's conclusion that Napolitano anticipates or renders obvious claims 1, 2, 4, 5, and 33–36.

Analysis

We find Appellants to have the better argument. The Examiner argues that Napolitano anticipates and/or render obvious the claims because it teaches "a hydrogel core surround by fibroblast cells or fibroblast and endothelial cells." (Ans. 15 (citations omitted).)

As Appellants point out, however, Napolitano teaches self-assembled cellular aggregates that form, e.g., spheroids in the bottom of the recess of a gel. (Appeal Br. 61; *see, e.g.*, Napolitano Abstract; 2089, left column; Figs. 1 and 2.) The Examiner has not explained how such spheroids would contain a hydrogel core given that they form in a *recess* of the gel.

In response to Appellants' argument, the Examiner argues that "there is no evidence in Napolitano that the spheres did not enclose a defined volume" and that "Napolitano teaches in the 200 μm wells expansion [of the cell aggregate] in the horizontal dimension was physically constrained by the hydrogel." (Ans. 42 (citations omitted).) We are not persuaded. First, Napolitano describes spheroids containing, for instance, a normal human fibroblast (NHF) core coated with human umbilical vein endothelial cells

(HUVECs). (Napolitano Abstract.) Thus, it is not clear that Napolitano discloses a "membrane" of cells that defines an "enclosed volume," much less a hydrogel core, rather than a solid spheroid of cells. In addition, given that Napolitano's spheroid cell aggregates are formed in the hydrogel well, it is unsurprising that they are constrained by the well size. The Examiner has not explained, however, how such constraint suggests that the spheroid contains a hydrogel core.

With respect to claims 33–36, we further agree with Appellants that the Examiner has not shown how Napolitano disclose "components of a cell assembled in three dimensions and organized to form a membrane," as required by claims 33 and 34, or a reservoir within an enclosed volume comprising volvox algae or an organized algae micro-colony, as required respectively by claims 35 and 36. Neither has the Examiner provided a response to Appellants' arguments with respect to these claims.

Accordingly, we reverse the Examiner's rejection of claims 1, 2, 4, 5, and 33–36 as anticipated by Napolitano. Because the Examiner has not articulated any separate rationale why the above-discussed claim limitations are rendered obvious by Napolitano, we also reverse the Examiner's rejection of claims 1, 2, 4, 5, and 33–36 as obvious over Napolitano.

SUMMARY

With respect to the rejection under 35 U.S.C. § 101, we affirm the rejection of claims 1–4, 7, and 35 and reverse the rejection of claims 33, 34, and 36.

With respect to the rejection under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, for failure to comply with the written

description requirement, we affirm the Examiner's rejection of claims 1–5, 7, 8, and 13.

With respect to the rejection under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, for failure to comply with the enablement requirement, we affirm the Examiner's rejection of claims 1–5, 7, 8, 13, and 31–36.

With respect to the rejection under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Zetter, we affirm the Examiner's rejection of claims 1, 2, 4, and 7 and reverse the Examiner's rejection of claims 33 and 34.

With respect to the rejection under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Debnath, we affirm the Examiner's rejection of claims 1, 2, 4, and 7 and reverse the Examiner's rejection of claims 33 and 34.

With respect to the rejection under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Kirk, we affirm the Examiner's rejection of claims 1, 2, 4, 7, and 35 and reverse the Examiner's rejection of claims 33, 34, and 36.

We reverse the Examiner's rejection of claims 1, 2, 4, 5, and 33–36 under pre-AIA 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under pre-AIA 35 U.S.C. § 103(a) as obvious over, Napolitano.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

CERTIFICATE OF COMPLIANCE

This brief complies with the word-length limitation of Federal Circuit Rule 32(a). This brief contains 13,305 words, excluding the portions set forth in FRAP 32(f) and Federal Circuit Rule 32(b). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft® Word and 14-point Century type.

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Dated: September 25, 2017

CERTIFICATE OF SERVICE

I hereby certify that on this day, September 27, 2017, the foregoing was electronically filed and therefore served electronically via the court's ECF/CM system on all counsel of record.

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